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Zinc(II)-mediated diastereoselective Passerini reactions of biocatalytically desymmetrised renewable inputs†

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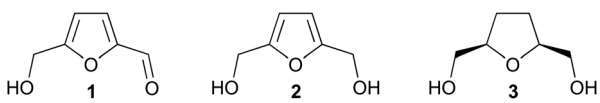
2,5-Bis(hydroxymethyl)tetrahydrofuran, a renewable building block, has been efficiently desymmetrised to give either enantiomers of the corresponding monobutyrate in high ee exploiting a biocatalytic methodology. The aldehydes derived from these monoesters have been subjected to a series of diastereoselective Passerini reactions. Careful optimization of reaction conditions has allowed for the increase of the dr from 1.5 : 1 to 9 : 1. The best results were obtained with zinc(II)-mediated reactions. In particular, a new modification of Passerini reaction that employs zinc dicarboxylates has been introduced.

Introduction

While most organic syntheses still rely on building blocks derived from oil or other fossil feedstock, there is a growing awareness that the scientific community should make all efforts to shift to renewable sources instead.[1–3] Moreover, Europe, the USA and other countries are implementing fiscal incentives to promote the production of bio-based materials and fine chemicals. The most abundant and useful biomass is certainly wood, which, importantly, is not in competition with food crops. According to a list recently published by the US Department of Energy (DOE),[4] 5-hydroxymethylfurfural (5-HMF) **1** is one of the twelve most important building blocks that can be obtained from lignocellulosic biomass (Scheme 1). It is indeed derived from acid dehydration of hexoses.[5] An oxidized derivative of **1** (2,5-furandicarboxylic acid) is already used for the production of a new bio-based polyester which is expected to replace PET for beverage plastic bottles.[4] On the other hand, catalytic hydrogenation of **1** furnishes, depending on the reaction conditions, either 2,5-bis(hydroxymethyl)furan **2** or *cis*-2,5-bis(hydroxymethyl)tetrahydrofuran (BHMTHF, **3**) (Scheme 1).[6,7] The latter has already found practical applications as a solvent, monomer, and also for the production of various high-value chemicals such as 1,6-hexanediol and caprolactam.[7,8] However, its use as starting material for more complex, chiral products, *e.g.* heterocycles, is still largely unexplored.

Some of us have been involved, in recent years, in the transformation of renewable building blocks into complex heterocyclic systems,[9] applying "green" methodologies. For this purpose, we are taking advantage of the powerful integration of multicomponent reactions (MCRs) with biocatalysis. This fruitful combination[10] was first proposed by Ostaszewski and coworkers[11] and since then used by various research groups,[12–17] including ours.[18–29]

From a green chemistry perspective, while the use of renewable starting materials, the implementation of MCRs[30] and the practice of biocatalysis[31–33] all represent desirable approaches, the union of these three in a single integrated, general strategy can boost their individual beneficial impact on sustainable synthesis. In this paper, we provide an example of this strategy, which makes use of biocatalysis as well as the Passerini multicomponent reaction for the stereoselective transformation of BHMTHF (**3**) into chiral, relatively complex, depsipeptides. Also disclosed herein are modification of the Passerini reaction, based on the use of zinc derivatives.



Scheme 1 5-HMF **1** and its derivatives.

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Results and discussion

We first studied the enzymatic desymmetrization of BHMTHF **3**.

For the laboratory scale preparation of **3**, a diol industrially produced by hydrogenation of **1** under high pressure,[7] we performed the diastereoselective oxidation of 1,5-hexadiene using $NaIO_4$ under the catalysis of $RuCl_3$ as reported by Stark and coworkers.[34] The enzymatic monoacylation of **3** was not previously reported while the enzymatic monohydrolysis of its diesters,[35] such as dibutyrate **5** or the corresponding diacetate, was known.[36–38] After a series of thorough optimization studies, we found that this desymmetrization could be best performed using vinyl butyrate in diisopropyl ether at 0 °C, with the catalysis of Amano PS lipase supported on Celite (Scheme 2).[39] Under these conditions, monobutyrate (−)-**4** was obtained in good isolated yield (80%) with an excellent ee of 96%.

However, on scaling up the reaction to multigram quantities, the reaction turned out to be rather erratic. Although the ee remained high, the reaction time needed to reach the desired conversion (50–55%) varied significantly (from a few hours to more than a day), depending on the batch of the diol employed. Eventually, we found that use of a 4 : 1 iPr_2O–CH_2Cl_2 mixture as the cosolvent and addition of powdered 3 Å molecular sieves rendered the process highly reproducible. Under these optimized conditions, the reaction provides 96% ee at 50% conversion[40] (82% yield) or 99% ee at 59% conversion[40] (72% yield).

In order to have access to the opposite enantiomer as well, we next studied the enzymatic hydrolysis of diesters of **3**. With the diacetate using different enzymes, the maximum ee was only 86% in our hands. In contrast, a satisfactory ee of 92.4% was obtained in the reaction of dibutyrate **5** using Amano M lipase from *Mucor javanicus*, an observation in line with the previous work by Prasad and coworkers.[37]

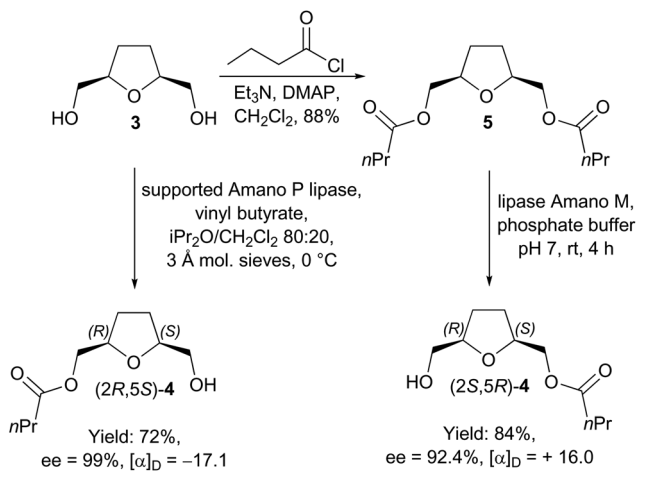
Thus, both enantiomers of **4** were accessible in high ee, of which the (−)-enantiomer derived from the enzymatic acylation, was used for the subsequent study on application in multicomponent reactions. Among the various MCRs, the Passerini reaction was selected for use of the renewable chiral building block **4**. Thus, we investigated the sequence of oxidation of (−)-**4** and reaction of **6** (Table 1). Initially, following our previous work on desymmetrized erythritol derivatives,[22] we used a one-pot protocol, in which **4** was oxidized with catalytic TEMPO and stoichiometric $PhI(OAc)_2$ and treated with *tert*-butyl isocyanide. In this *in situ* Passerini process, in which the acetic acid by-product from the $PhI(OAc)_2$ oxidant acted as the carboxylic component, acetoxy amide **7a** was produced in excellent yield, but with poor diastereoselectivity (<1.5 : 1) (entry 1, Table 1). Since the reaction was quite fast, we hoped to increase the dr by lowering the temperature. However, performing the reaction at −78 °C gave no improvement, leading only to a decrease of the isolated yield (entry 2). It was also found that the solvent had only little influence on the dr (entries 3–6).

We then decided to investigate the possible beneficial effect of a Lewis acid additive. We reasoned that the Lewis acid could be chelated by the carbonyl and ethereal oxygen atoms of **6**, leading to a more rigid transition state.[42] In the event, as noted in our previous work on erythritol derivatives,[22] zinc halides emerged as efficient promoters, with $ZnBr_2$ being the best (entry 10 *vs.* entries 7 and 8).

A series of solvent screening experiments was then performed, in which remarkable increase of diastereoselectivity was noted on going from CH_2Cl_2 (entry 11) to ethereal solvents, especially diisopropyl ether (entry 14). Interestingly, addition of 10% cosolvent turned out to be slightly deleterious (entry 15) while reducing catalyst loadings from 1 to 0.4 equivalents did not lower the diastereoselectivity or yield (entry 16).

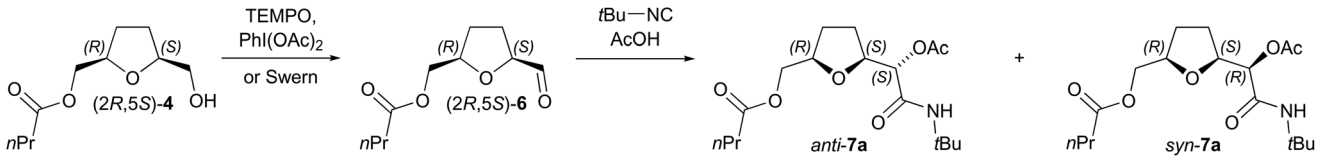
Next, we investigated the effect of the order of addition of the reagents. Based on our initial hypothesis that the role of the zinc reagent might be chelation with aldehyde **6**, we tried slow addition of the isocyanide (or the mixture of the isocyanide and carboxylic acid) to a premixed solution of aldehyde **6** and $ZnBr_2$ (entry 17). However, to our surprise, this led to decrease in both the dr and yield. We eventually found that the optimal procedure, unexpectedly, involved slow addition of the aldehyde and carboxylic acid mixture to the premixed solution of the isocyanide and $ZnBr_2$ despite longer reaction times (entries 19 and 20).

In practicing the procedure on preparative scales, however, the yields of both the oxidation and Passerini reactions were found to be highly variable. Noting the strong tendency of aldehyde **6** to form a hydrate, likely stabilized by the adjacent THF oxygen, we surmised that the presence of water might cause the over-oxidation and lower the yield of the $ZnBr_2$ catalysed Passerini reaction. Indeed, performing the oxidation using the Swern methodology gave a nearly quantitative yield of the aldehyde. In addition, we found further drying of the aldehyde by freshly activated molecular sieves or azeotropic removal of water to be beneficial. Under these optimized conditions, the two-step reaction became reproducible, giving rise to **7a** as a 81 : 19 mixture of *anti* and *syn* diastereomers (entry



Scheme 2 Desymmetrization of *meso* diol **3** and diester **5**.

Table 1 Optimization of the diastereoselectivity in the Passerini reaction to give **7a** [a]



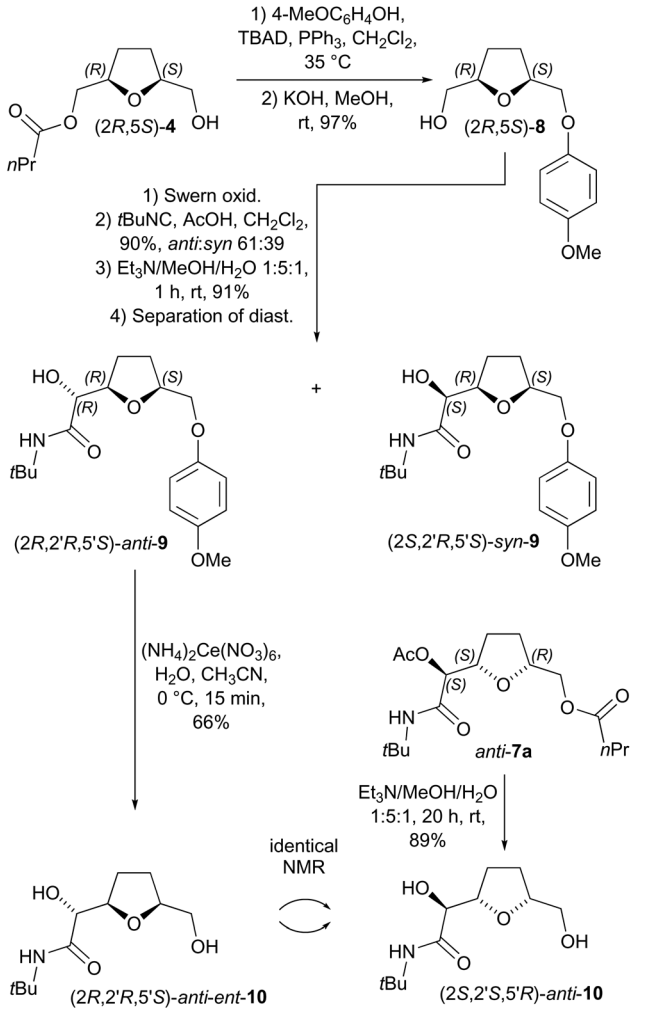
Entry	Prep. of **6** [b]	Solvent	Additive (equiv.)	Mode of addition[c]	Temp (°C)	Time (min)	Yield[d] (%)	dr (*anti* : *syn*)[e]
1	A	THF/CH_2Cl_2 1 : 1	None	D	20	40	93	59 : 41
2	A	THF/CH_2Cl_2 1 : 1	None	D	−78	205	27	58 : 42
3	B	CH_2Cl_2	None	D	20	60	96	59 : 41
4	B	THF	None	D	20	60	77	62 : 38
5	B	Et_2O	None	D	20	60	74	62 : 38
6	B	iPr_2O	None	D	20	90	94	62 : 38
7	A	THF/CH_2Cl_2 1 : 1	$ZnCl_2$ (1)	D	20	60	59	63 : 37
8	A	THF/CH_2Cl_2 1 : 1	ZnI_2 (1)	D	20	60	85	64 : 36
9	A	THF/CH_2Cl_2 1 : 1	ZnI_2 (1)	D	−78	120	36	65 : 35
10	A	THF/CH_2Cl_2 1 : 1	$ZnBr_2$ (1)	D	20	40	60	71 : 29
11	B	CH_2Cl_2	$ZnBr_2$ (1)	D	20	60	32	64 : 36
12	B	THF	$ZnBr_2$ (1)	D	20	60	56	71 : 29
13	B	Et_2O	$ZnBr_2$ (1)	D	20	60	78	72 : 28
14	B	iPr_2O	$ZnBr_2$ (1)	D	20	90	85	76 : 24
15	B	iPr_2O/THF 9 : 1	$ZnBr_2$ (1)	D	20	90	80	72 : 28
16	B	iPr_2O	$ZnBr_2$ (0.4)	D	20	120	85	76 : 24
17	B	iPr_2O	$ZnBr_2$ (0.4)	E	20	180	57	72 : 28
18	B	iPr_2O	$ZnBr_2$ (0.4)	F	20	180	68	80 : 20
19	B	iPr_2O	$ZnBr_2$ (0.4)	G	20	180	88	79 : 21
20	B	iPr_2O	$ZnBr_2$ (0.4)	G	20	180	77[f]	79 : 21
21	**C**	**iPr_2O**	**$ZnBr_2$ (0.4)**	**G**	**20**	**260**	**82**[f]	**81 : 19**

[a] This table shows some selected results, but the full set of optimization data can be found in the ESI.† [b] **A**: Oxidation was performed with TEMPO/PhI(OAc)$_2$, and the following Passerini reaction was carried out in a one-pot manner. Yield of both diastereomers determined based on alcohol **4**; **B**: oxidation was performed with TEMPO/PhI(OAc)$_2$, and aldehyde **6** was purified by chromatography. Yield based on aldehyde **6**; **C**: aldehyde **6** obtained from Swern oxidation was purified by chromatography and thoroughly dried over molecular sieves. Yield determined based on aldehyde **6**. [c] **D**: All reagents were added together; **E**: isocyanide added slowly (during 2 h) to the mixture of aldehyde, $ZnBr_2$ and carboxylic acid; **F**: aldehyde added slowly (during 2 h) to the mixture of isocyanide, $ZnBr_2$ and carboxylic acid; **G**: aldehyde and carboxylic acid mixed together and added slowly (during 2 h) to the mixture of isocyanide and $ZnBr_2$. [d] Overall yield of the two diastereomers. NMR yield was determined by ^{1}H NMR of the crude in the presence of 2,5-dimethylfuran as internal standard. [e] Determined by ^{1}H NMR analysis on the crude product. [f] Isolated yield.

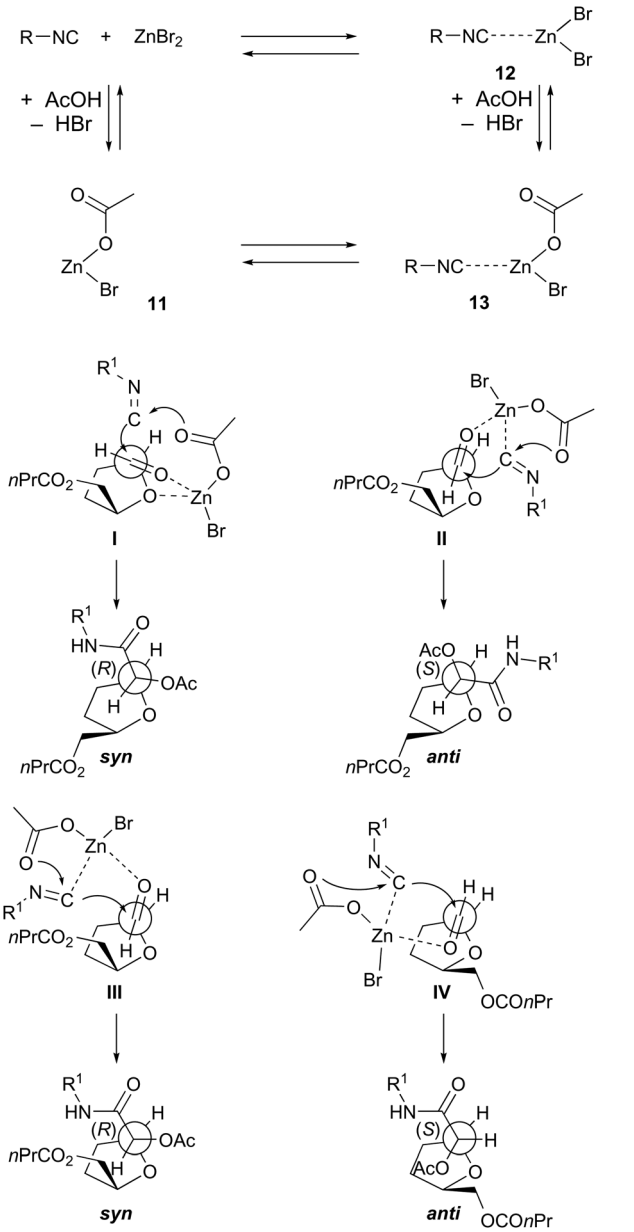
21). Thus, it was shown to be feasible to improve the diastereoselectivty of an isocyanide-based MCR, a process known for poor stereoselectivity, by modifying the reaction conditions.[22]

The results of entries 17, 19 and 20 (experiments regarding the order of addition of reagents) disputed our initial hypothesis of zinc(II) chelation. Furthermore, the stereochemical analysis of the major isomer contradicted this hypothesis. In order to determine the absolute configuration of the stereocenter formed by the Passerini reaction, our attempts were initially focused on the preparation of Mosher esters of the secondary alcohol of **7a**.[43] Due to the difficulty in selective deprotection, however, we turned to the synthesis of the PMP protected alcohol (2*R*,5*S*)-**8** from (2*R*,5*S*)-**4** by protecting group exchange as described in Scheme 3. Thus, the desymmetrised alcoholic ether (*cf.* **8**), rather than ester (*cf.* **4**), was subjected to the sequence of oxidation and Passerini reactions to give a mixture of *anti* and *syn* diastereomers, each of which was hydrolysed and reacted with both enantiomers of Mosher's chlorides. ^{1}H NMR analyses of these four Mosher's esters assigned the major diastereomer of **9** to be of (2*R*) (and thus *anti*) configuration and that of the minor diastereomer of **9** to be of (2*S*) (and thus *syn*) configuration. Then, *anti*-**9** was correlated to *anti*-**7a** *via* conversion into the corresponding diols (2*R*,2′*R*,5′*S*)-*anti*-*ent*-**10** and (2*S*,2′*S*,5′*R*)-*anti*-**10**, respectively. These two enantiomers gave superimposable NMR spectra, whereas the spectrum of *syn*-**10** was clearly different.[44]

Having established the stereochemical outcome, we revised our mechanistic rationale as shown in Scheme 4. This proposal is also based on the observation that $ZnBr_2$, which is usually insoluble in iPr_2O, is partly dissolved when mixed with *t*-butyl isocyanide. We believe that the formation of a complex such as **12** might represent the first step, which a recent report that $ZnBr_2$ could even form a complex with two isocyanides lends support to.[45] There could be an equilibrium between **12** and $ZnBr_2(CN\text{-}R)_2$, together with an exchange process with acetic acid that can lead to monoacetate **13**, which may be the real reacting species. With this backdrop, the chelated transition state **I**, which we initially hypothesized, would favour the *syn* product due to the steric encumbrance of the lower carbonyl face. Also in discord with the chelation model is the finding that pre-mixing $ZnBr_2$ and the aldehyde has a deleterious effect. Thus, it is more reasonable to assume that the zinc



Scheme 3 Determination of absolute configuration of the new stereogenic centre.

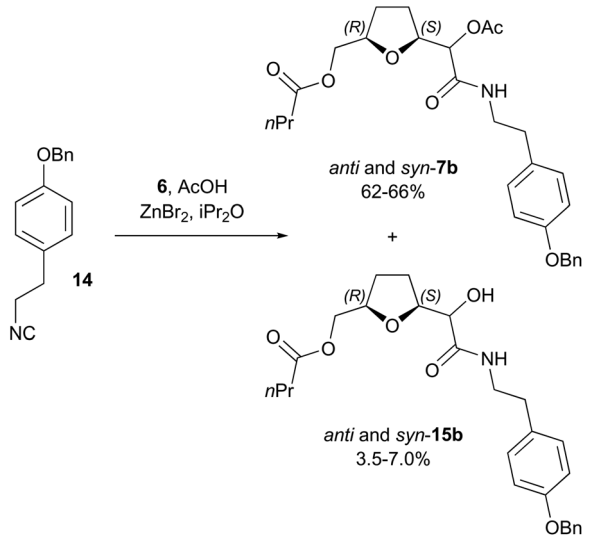


Scheme 4 Rationalisation of stereochemical results.

centre is coordinated by the aldehyde and the isocyanide, allowing a concerted intramolecular mechanism as shown in transition states **II–IV**. The formation of *anti* products could be preferred by a typical Felkin–Anh model such as **IV**. However, the butyryloxymethyl arm would impose a severe steric strain to the zinc catalyst. Moreover, the Felkin–Anh model is based on the Bürgi–Dunitz trajectory, whereas the trajectory in our case, if the concerted mechanism is operative, should be closer to 90°. Thus, we think that transition states **II** and **III**, with the aldehyde group placed "outside" the THF ring, would be more favoured. Again, the orientation of the butyryloxymethyl group is expected to favour **II**, leading to the *anti* isomer.

The same transition state is likely to be favoured under "normal" Passerini conditions, but the increased selectivity with the zinc modifications may be due to the more rigid transition states and the higher steric demand of the carboxylate group. The slow addition of the aldehyde and acid components may be beneficial, limiting the "normal" Passerini reaction. It should be noted that the rates of Passerini reactions are very similar with or without $ZnBr_2$ additive. In addition, involvement of two molecules of the carboxylic acid in the transition state has been put forward by the recent mechanistic studies by Morokuma *et al.*[46,47] Thus, high dilution of the carboxylic acid, a possible setting under condition **G** (entries 19–21, Table 1), may be beneficial in suppressing the "normal" mechanism.

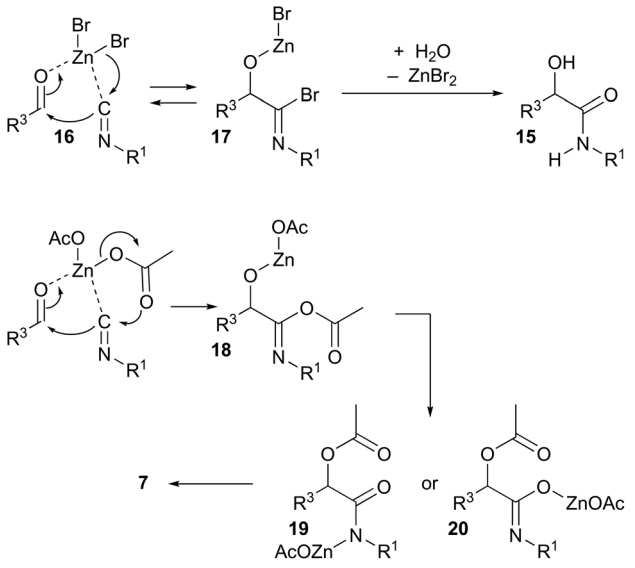
Having found the optimal conditions for the model system, we set out to examine the isocyanide and carboxylic acid components. Our effort to expand the scope of the reaction, however, met with two problems: (1) poor solubility of several carboxylic acids in iPr_2O and (2) formation of side-products. In particular, as shown in Scheme 5, alcohol side-product **15b**,



Scheme 5 Formation of truncated Passerini adducts.

albeit formed in small amounts (3.5–7%), posed major difficulty in the analysis of the reaction outcome and purification of the product.[48] The dryness of aldehyde **6** was found to affect the yield of the alcohol diastereomers **15b**. Interestingly, the dr was about 1 : 1, indicating that they did not derive from a hydrolysis of **7a**, but, instead, from an independent process. While these side-products were never detected under classical Passerini conditions, Lewis acids were known to promote the generation of these so-called "truncated" Passerini products without incorporation of a carboxylic acid *via* the intermediacy of **17** as shown for $ZnBr_2$ (Scheme 6).[49]

Based on this rationale, we decided to investigate the use of a preformed zinc carboxylate. It was anticipated that such a zinc salt could promote the reaction while suppressing both the "normal" and "truncated" Passerini reactions. Free from these two reactions, the factors affecting the reaction (solvent, slow addition, *etc*.) could be less important. Thus, the optimization study on the reaction in Scheme 5 was performed using isocyanide **14** and acetic acid (entries 4–6, Table 2). With stoichiometric $Zn(OAc)_2$ (condition C) instead of catalytic $ZnBr_2$ (condition B), the reaction was considerably slower, in part because of the insolubility of $Zn(OAc)_2$ in organic solvents. However, the formation of truncated products was almost completely suppressed, especially when aldehyde **6** was thoroughly dried over molecular sieves. Moreover, the diastereoselectivity was essentially the same, with the yield of **7b** higher. A possible mechanism is shown in Scheme 6.



Scheme 6 Putative mechanism of the zinc dicarboxylate modification.

A set of solvent screening studies revealed $CHCl_3$ to be optimal for the reaction with zinc acetate at 40 °C for 4.5 h. The work-up conditions were found to be important to obtain high yield. At the end of the reaction, treatment of the precipitates with 1 M HCl prior to extraction was necessary for complete recovery of the material, presumably because the release of **7b** from the zinc derivative **19** or **20** required an acid.

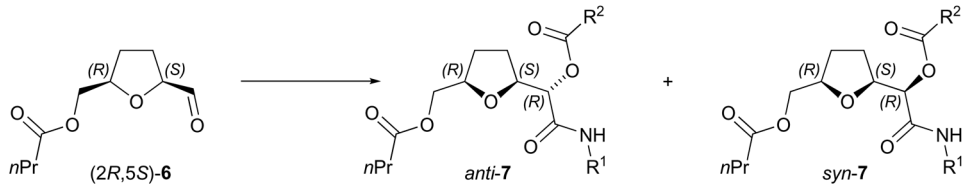
The slower rate, compared to that of the $ZnBr_2$ catalyzed process, could be due to the poor solubility of $Zn(OAc)_2$ and also to its milder Lewis acid character, which might influence the complexation equilibrium with the isocyanide and/or the aldehyde. In the case where 0.4 equivalents of $Zn(OAc)_2$ and stoichiometric acetic acid were used, the reaction was much faster but gave a 62 : 38 dr, suggesting that the normal Passerini mechanism competed significantly with the zinc-mediated pathway.

In addition to the advantage of diastereoselection over the standard Passerini conditions, the new Passerini reaction with unprecedented modification is advantageous over the $ZnBr_2$ catalyzed process: (a) "truncated" Passerini products are nearly suppressed; (b) it is possible to use $CHCl_3$ solvent capable of dissolving a broad range of reactants; (c) the reaction can be performed without the need of slow addition; (d) in some cases the diastereoselectivity may be higher. The disadvantages are: (a) the need to prepare the zinc carboxylates that are not commercially available; (b) only half of the carboxylic acid is incorporated in the product.

The scope of the reaction employing zinc carboxylates was then assessed using different isocyanides and carboxylic acids (Table 2, method C). For some entries, the reactions under the classical Passerini conditions (method A) and/or under the $ZnBr_2$ catalyzed methodology (method B) are presented for comparison. In nearly all instances, method C is superior to the $ZnBr_2$ catalysed reaction in terms of the yield and the ability to suppress the "truncated" Passerini side products.

The two modified protocols employing zinc additives provide significant improvement in the diastereoselectivity *vis-à-vis* the standard Passerini conditions. Method C is particularly more effective with aromatic carboxylates and isocyanides bearing primary alkyl groups, thus giving a better result than other methods (*cf.* entries 7–9). The higher diastereoselection achieved with aromatic (bulkier) carboxylates agrees with the

Table 2 Scope of the modified Passerini reaction to give esters 7



Entry	Product	R^1	R^2	Method[a]	Time[b] (min)	Yield[c] (%)	dr (*anti* : *syn*)[d]
1	**7a**	*t*Bu	Me	A	40	90	59 : 41
2	**7a**	*t*Bu	Me	B	260	82	81 : 19
3	**7a**	*t*Bu	Me	C	285	74	71 : 29
4	**7b**	(4-BnO-C_6H_4)CH_2CH_2	Me	A	60	87	58 : 42
5	**7b**	(4-BnO-C_6H_4)CH_2CH_2	Me	B	150	64	73 : 27
6	**7b**	(4-BnO-C_6H_4)CH_2CH_2	Me	C	260	79	76 : 24
7	**7c**	*n*Bu	Ph	A	120	90	66 : 34
8	**7c**	*n*Bu	Ph	B	240	52	76 : 24
9	**7c**	*n*Bu	Ph	C	260	71	90 : 10
10	**7d**	Bn	Me	B	240	52	83 : 17
11	**7d**	Bn	Me	C	285	76	79 : 21
12	**7e**	4-(Allyloxy)-C_6H_4	Me	B	120	68	82 : 18
13	**7e**	4-(Allyloxy)-C_6H_4	Me	C	255	87	82 : 18
14	**7f**	Me	Ph	C	90	77	86 : 14
15	**7g**	(4-BnO-C_6H_4)CH_2CH_2	Ph	C	240	77	84 : 16
16	**7h**	Cyclohexyl	$PhCH_2CH_2$	C	320	84	74 : 26
17	**7i**	*t*Bu	$PhCH_2CH_2$	C	270	78	70 : 30
18	**7j**	1,6-Di-Me-C_6H_4	*ortho*-MeC_6H_4	C	225	77	84 : 16
19	**7k**	*t*Bu	*ortho*-MeC_6H_4	C	260	60	63 : 37
20	**7l**	*n*Bu	*ortho*-MeC_6H_4	C	220	78	82 : 18

[a] **A**: Standard Passerini reaction with no additives in CH_2Cl_2 at rt; **B**: slow addition, at rt, of the mixture of aldehyde **6** and carboxylic acid to the isocyanide premixed with 0.4 equivalents of $ZnBr_2$ in iPr_2O; **C**: reaction of **6** with the isocyanide and the appropriate zinc dicarboxylate, in $CHCl_3$ at 40 °C. In all cases, aldehyde **6** was chromatographed and then thoroughly dried by overnight treatment with molecular sieves or azeotroping with toluene. [b] Reaction were stopped when starting aldehyde completely disappeared. For this reason, reaction times differ depending on reaction conditions and on substrates. [c] Isolated overall yield of both diastereomers. [d] Determined by ^1H NMR analysis of the crude product.

rationalization shown in Scheme 4. On the other hand, with *tert*-butyl isocyanide diastereoselectivities are slightly lower using method C compared to method B (entries 2 and 3 *vs.* entry 17). For other combinations, the dr values obtained with methods B and C are similar, but the reactions carried out with method C are cleaner.

In order to gain more insights in the stereochemical outcome of the reaction, we carried out theoretical calculations by using DFT (see Experimental part). First, the conformational analysis of **6** has been performed, revealing that the conformer bearing the aldehyde group "outside" the THF ring (Scheme 4, T.S. **II** and **III**) was the most favoured. Then, this conformation was used to build a model of the possible transition states including **6**, zinc acetate and methyl isocyanide. Our results clearly showed that T.S. **II**, in which the coordinated isocyanide attacks from the opposite face respect to the tetrahydrofuran ring, is favoured (Fig. 1A). Even when the isocyanide is placed in the opposite position (as showed in the T.S. **III**), the optimization calculations converge on the structures where isocyanide occupies an equivalent position. Moreover, the simple observation of the conformations assumed by **6** in the T.S. **II** model, in which the atoms are represented by vdW spheres, clearly suggests that this preference is due to the steric hindrance produced by the hydrogen atoms of the CH_2 groups present on the tetrahydrofuran ring, rather than the presence of the butyryloxymethyl group (Fig. 1B). Based on a recent computational analysis,[47] where the authors proposed that the formation of the nitrilium complex (Fig. 1C) is the rate-determining step of the reaction, we have calculated the potential energy profile for the attack of the methyl isocyanide to aldehyde **6**. As illustrated in Fig. 1D, the energy barrier to be overcome to obtain the nitrilium intermediate is 11.9 kcal mol^{-1}, demonstrating the feasibility of the process.

The Passerini products described above have two masked protected alcoholic moieties that can be exploited for further structural elaborations (Scheme 7). First, selective removal of the butyryl group from **7a** was accomplished to form **21** by enzymatic hydrolysis using *Candida antarctica* lipase B (CAL-B). In contrast to our previous findings concerning the erythritol derivatives,[22] the acetyl group displayed much less tendency to migrate from the secondary to the primary alcohol. The diastereomeric mixture of Passerini products **7a** was also hydrolyzed into diols **10**, which were converted directly into bicyclic systems **22** by applying Mitsunobu conditions. The diastereomeric ratio was conserved in this stereospecific process (*anti*-**7a** to *anti*-**22**), due to the selective substitution at the primary alcohol, as observed in our previous work on erythritol derivatives.[22]

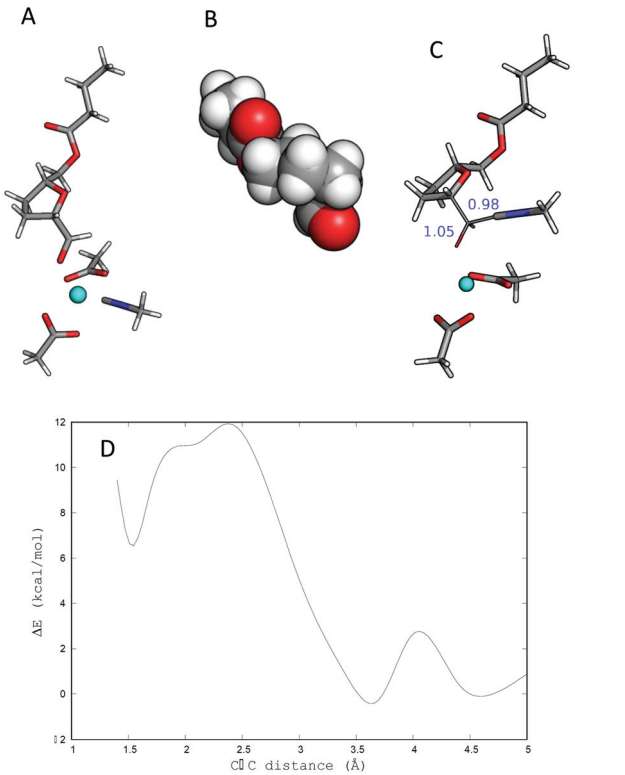
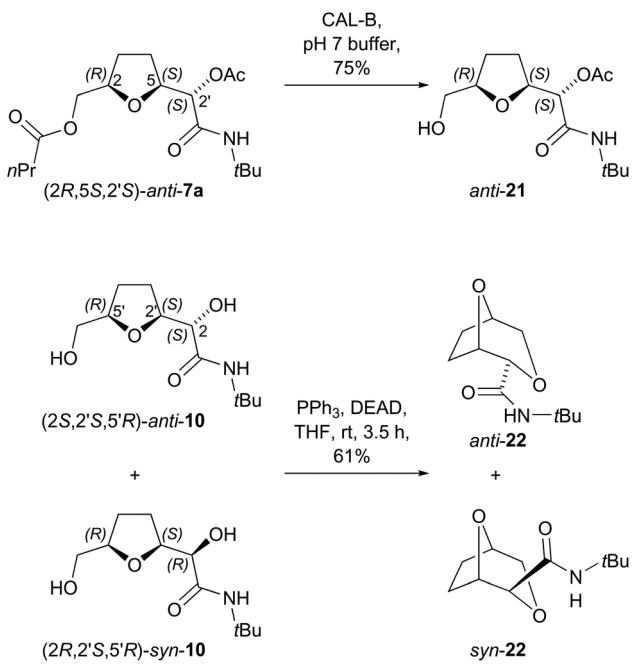


Fig. 1 (A) Optimized structures of the energetically favored model built including aldehyde **6**, zinc diacetate and methyl isocyanide. (B) Representation of the most favoured conformation assumed by **6** represented using vdW spheres. (C) Structure of the reaction intermediate obtained by RPES calculations corresponding to the energy minimum at 1.5 Å. The bond more critical for the formation of the intermediate are showed as smaller sticks and the corresponding Wiberg bond orders are reported. (D) Energy profile from RPES calculations.



Scheme 7 Some transformations carried out on Passerini products.

Conclusions

Despite the fact that the Passerini reaction is nearly 100 years old, very few studies regarding the diastereoselectivity, when using chiral aldehydes, have appeared in the literature. With the exception of few cases, poor levels of stereoinduction have been reported.[22,50] In this paper, we have found that it is possible to achieve significant enhancement in the diastereoselectivey by optimizing reaction conditions. In particular, we have introduced a new way to perform the Passerini reaction, using zinc carboxylates. This new modification may be advantageous with improved diastereoselectivities and of use in difficult cases where the normal conditions fail. Studies are in progress to find other useful applications of this new modification and to apply it to the Ugi reaction.

Experimental section

General methods

NMR spectra were taken at rt in $CDCl_3$ at 300 or 500 MHz (^1H), and 75 or 126 MHz (^{13}C), using, as internal standard, TMS (^1H NMR: 0.000 ppm) or the central peak of $CDCl_3$ (^{13}C: 77.02 ppm). Chemical shifts are reported in ppm (δ scale). Peak assignments were made with the aid of gCOSY, gHSQC and gHMBC experiments. HPLC-MS-UV analyses were carried under inverse phase with a Phenomenex Gemini 3μ C6-Phenyl (150 × 3 mm) column. Detectors: DAD (226 nm), and MS Microsaic 4000 MiD (ESI ionization, Tic voltage 750, single quadrupole, FullScan: 100–800 m/z). Quantitative determination was done with DAD detector, while MS was used to recognize Passerini and "truncated" Passerini products. Column temp: 30 °C. Flow: 0.34 mL min^{-1}. Elution was done with A : B from 90 : 10 to 0 : 100, where (A) = H_2O + 1% formic acid; (B) = CH_3CN + 1% formic acid. HRMS: samples were analysed with a Synapt G2 QToF mass spectrometer. MS signals were acquired from 50 to 1200 m/z in ESI positive ionization mode. TLC analyses were carried out on silica gel plates and viewed at UV (254 nm) and developed with Hanessian stain (dipping into a solution of $(NH_4)_4MoO_4$ 4 H_2O (21 g) and Ce $(SO_4)_2$ 4 H_2O (1 g) in H_2SO_4 (31 ml) and H_2O (469 ml) and warming) or with $KMnO_4$. R_f were measured after an elution of 7–9 cm. Column chromatographies were done with the "flash" methodology using 220–400 mesh silica. Petroleum ether (40–60 °C) is abbreviated as PE. In extractive work-up, aqueous solutions were always reextracted three times with the appropriate organic solvent. Organic extracts were always dried over Na_2SO_4 and filtered, before evaporation of the solvent under reduced pressure. All reactions using dry solvents were carried out under a nitrogen atmosphere.

((2*R*,5*S*)-5-(Hydroxymethyl)tetrahydrofuran-2-yl)methyl butyrate (−)-4. A solution of diol **3** (2.00 g, 15.13 mmol) in dry diisopropyl ether (113 mL) and dry methylene chloride (28 mL), was treated with vinyl butyrate (9.60 mL, 75.65 mmol) and freshly activated 3 Å powdered molecular sieves (757 mg). The mixture was cooled to 0 °C and treated with Amano PS lipase,

supported on Celite as previously described[39] (800 mg, corresponding to 178.4 mg of unsupported enzyme). The suspension was stirred until disappearance of starting diol, as judged by TLC. This corresponds to a conversion of about 58–60%, where conversion is defined as the percentage of acylated hydroxy groups. Thus conversion = ([**5**]*2 + [**4**])/[starting **3**]*2. Typically, this conversion (which can be determined precisely by ^{1}H NMR of the crude product) is reached after 20 h. The crude product was filtered through a sintered funnel, washed with EtOAc/MeOH 9 : 1. In this way, the supported enzyme could be easily recovered and reused, without loss of activity (at least for three times). After evaporation of the mother liquors, chromatografy (PE/EtOAc from 3 : 2 to 1 : 1) gave pure monobutyrate (−)-**4** as a liquid (2.20 g, 72%). Ee was 99%, as determined by HPLC of the corresponding benzoate on a chiral stationary phase. Conditions: column Daicel Chiral Pak AD (250 × 4.6 mm); detector DAD (226 nm). Isocratic elution with *n*-hexane/isopropanol 95 : 5. Temperature: 26 °C. R_t (−) enantiomer: 23.98 min. R_t (+) enantiomer: 22.65 min. $[\alpha]_D$ = −17.1 (*c* 1.09, toluene). $[\alpha]_D$ = −6.3 (*c* 1.0, $CHCl_3$). Lit. (for the (+) enantiomer): +16.0 (toluene).[37] R_f 0.22 (PE/EtOAc 7 : 3). ^{1}H NMR (300 MHz, $CDCl_3$, 20 °C): δ = 4.25–4.05 (4 H, m, C*H*$_2$OC═O, 2-H, 5-H), 3.74 and 3.50 (2 H, AB part of ABX syst., J_{AB} = 11.8 Hz, J_{AX}, J_{BX} = 4.9, 3.1 Hz, C*H*$_2$OH), 2.80 (1 H, br s, O*H*), 2.34 (2 H, t, *J* = 7.4 Hz, C*H*$_2$C═O), 2.09–1.64 (4 H, m, 3-*H*, 4-*H*), 1.66 (2 H, hexuplet, *J* = 7.2 Hz, CH_3CH_2), 0.96 (3 H, t, *J* = 7.3 Hz, C*H*$_3$). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 173.8 (*C*═O), 80.4, 77.4 (C-2, C-5), 66.2 (*C*H$_2$OCO), 64.5 (*C*H$_2$OH), 36.1 (*C*H$_2$C═O), 28.0, 26.7 (C-3, C-4), 18.4 (*C*H$_2$CH$_3$), 13.6 (*C*H$_3$–CH$_2$). I.R. (ATR): ν_{max} 3450, 2964, 2876, 1733, 1459, 1381, 1305, 1254, 1176, 1078, 1046, 995, 942, 884, 815, 752, 709, 610 cm^{-1}. GC-MS: R_t 6.43 min. *M*/*z*: 171 (M^+ − 31, 19%), 114 (8.2), 101 (50), 89 (9.0), 84 (15), 83 (95), 71 (100), 69 (5.8), 59 (6.7), 58 (5.7), 57 (62), 56 (5.1), 55 (45), 45 (5.8), 44 (8.9), 43 (89), 42 (14), 41 (29), 39 (12). HRMS (ESI+): found 203.1287 [calcd for $C_{10}H_{19}O_4^+$ $(M + H)^+$ 203.1283].

((2*R*,5*S*)-5-(Butyryloxymethyl)tetrahydrofuran-2-yl)methyl butyrate 5. A solution of diol **3** (660 mg, 5 mmol) in dry CH_2Cl_2 (50 mL) was cooled to 0 °C and treated with Et_3N (3.0 mL, 20 mmol), 4-dimethylaminopyridine (61 mg, 0.5 mmol) and butyryl chloride (1.24 mL, 12 mmol). The mixture was stirred for 1 h at 0 °C and for 3 h at rt. Then it was poured into saturated aqueous $NaHCO_3$ (70 mL). The phases were separated, and the aqueous phase re-extracted twice with Et_2O. The united organic extracts were washed with brine, evaporated and chromatographed (PE/EtOAc from 4 : 1 to 3 : 2) to give known[37] dibutyrate **5** as a liquid (1.55 g, 88%). R_f = 0.70 (PE/EtOAc 1 : 1). ^{1}H NMR (300 MHz, $CDCl_3$, 20 °C): δ = 4.15–4.07 (4 H, m, C*H*HOC═O, 2-H, 5-H), 3.95 (2 H, dd, *J* = 12.4 Hz, *J* = 7.1 Hz, C*H*HOC═O), 2.26 (2 H, t, *J* = 7.4 Hz, C*H*$_2$C═O), 2.00–1.86 (1 H, m, 3-H or 4-H), 1.70–1.50 (3 H, m, 3-H or 4-H), 1.59 (4 H, hexuplet, *J* = 7.5 Hz, CH_3CH_2), 0.88 (6 H, t, *J* = 7.4 Hz, C*H*$_3$). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 173.3 (*C*═O), 77.2 (C-2, C-5), 65.9 (*C*H$_2$O), 35.8 (*C*H$_2$C═O), 27.5 (C-3, C-4), 18.2 (*C*H$_2$CH$_3$), 13.4 (*C*H$_3$).

((2*S*,5*R*)-5-(Hydroxymethyl)tetrahydrofuran-2-yl)methyl butyrate (+)-4. Diburyrate **5** (224 mg, 0.82 mmol) was suspended in 0.5 M pH 7 phosphate buffer (KH_2PO_4/K_2HPO_4) (12 mL) and treated with Amano M lipase (23 mg). The mixture was vigorously stirred for 4 h at rt. Then it was saturated with solid NaCl, diluted with EtOAc, and filtered through a Celite cake. After separation of the phases, the aqueous one was re-extracted twice with EtOAc. The organic extracts were chromatographed (PE/EtOAc from 3 : 2 to 1 : 1) to give pure (+)-**4** as a liquid (846 mg, 84%). $[\alpha]_D$ = +16.0 (*c* 1.02, toluene). The other data were identical to those of (−)-enantiomer. The ee was determined to be 92.4% by HPLC analysis (for conditions see the preparation of (−)-**4**).

((2*R*,5*S*)-5-Formyltetrahydrofuran-2-yl)methyl butyrate 6. A solution of dry DMSO (440 μL, 6.18 mmol) in dry CH_2Cl_2 (15 mL) was cooled to −78 °C and treated with a 2 M solution of oxalyl chloride in CH_2Cl_2 (2.6 mL, 5.2 mmol). After 10 min, a solution of alcohol (−)-**4** (500 mg, 2.47 mmol) in dry CH_2Cl_2 (6 mL) was added. After 10 min, triethylamine (1.60 mL, 12.0 mmol) was added. After 1 h, when the reaction was judged complete by TLC, the solution was poured into 30 mL of 5% aqueous $(NH_4)H_2PO_4$ + 2 mL of 1 M HCl. The phases were separated, and the aqueous phase re-extracted twice with Et_2O. The organic phases were washed with saturated aqueous $NaHCO_3$ and brine. After evaporation, the crude product was chromatographed (PE/EtOAc 3 : 2) to give, in quantitative yield, aldehyde **6** as an oil. This aldehyde was used as such for the Passerini reaction. An analytical sample was obtained by chromatography on thoroughly dried silica gel. ^{1}H NMR (500 MHz, $CDCl_3$, 20 °C): 9.70 (1 H, d, *J* = 1.6 Hz, C*H*═O), 4.37–4.30 (2 H, m, C*H*–O), 4.27 (1 H, dd, *J* = 11.7, 3.5 Hz, C*H*HO), 4.10 (1 H, dd, *J* = 11.7, 5.9 Hz, C*H*HO), 2.34 (2 H, t, *J* = 6.1 Hz, C*H*$_2$C═O), 2.22–2.02 (3 H, m, 3-H, 4-H), 1.72–1.61 (1 H, m, 3-H or 4-H), 1.67 (2 H, sextuplet, *J* = 7.1 Hz, CH_3CH_2), 0.96 (3 H, t, *J* = 7.5 Hz, C*H*$_3$). ^{13}C NMR (126 MHz, $CDCl_3$, 25 °C, acquired in J-MOD pulse sequence): δ 173.5 (*C*═O), 83.6 (*C*HO), 78.6 (*C*HO), 65.9 (*C*H$_2$O), 36.0 (*C*H$_2$C═O), 27.64, 27.57 (C-3, C-4), 18.4 (*C*H$_2$CH$_3$), 13.6 (*C*H$_3$). I.R. (ATR): ν_{max} 2964, 1732, 1458, 1381, 1364, 1306, 1259, 1178, 1082, 1049, 1001 cm^{-1}. HRMS (ESI+): found 201.1121 [calcd for $C_{10}H_{17}O_4^+$ $(M + H)^+$ 201.1127].

Typical procedure for preparation of zinc carboxylates: zinc(II) 2-methylbenzoate. NaOH (310 mg, 7.76 mmol) is dissolved in deionised water (5 mL) and added, under vigorous stirring, with 2-methylbenzoic acid (1.06 g, 7.76 mmol). After a while, a clear solution is obtained. Then, a solution of zinc(II) chloride (529 mg, 3.88 mmol) in deionized H_2O (2 mL) is slowly dropped. The precipitation of a white solid is observed. The flask containing the zinc chloride solution is washed twice with 0.5 mL of water, in order to transfer quantitatively the salt. After stirring for 2 h, the suspension is left standing overnight without stirring. The solid is recovered by filtration on a Büchner funnel and dried in a dessiccator under vacuum over P_4O_{10}. Yield: 1.06 g, 81%. White solid. M.p. = 233.8–235.2 °C. I.r.: ν_{max} 3064, 2969, 2930, 1625, 1605, 1577, 1525, 1434, 1397, 1288, 1199, 1161, 1105, 1051, 1035, 955, 875, 855, 815, 786, 734, 700, 665 cm^{-1}.

Using the same procedure we prepared **zinc benzoate** (m.p. = 313.9–316.2 °C. I.r.: ν_{max} 3062, 3031, 1979, 1914, 1823, 1631, 1595, 1576, 1539, 1526, 1494, 1403, 1312, 1175, 1158, 1102, 1070, 1027, 1003, 976, 938, 865, 842, 819, 712, 695, 684, 675, 606 cm^{-1}) and **zinc phenylpropionate** (m.p. = 158.1–160.6 °C. I.r.: ν_{max} 3061, 3031, 2978, 2921, 2866, 1599, 1531, 1498, 1468, 1439, 1404, 1354, 1284, 1251, 1163, 1080, 1031, 960, 910, 832, 784, 749, 730, 697 cm^{-1}.

General conditions for the Passerini reaction. ((2*R*,5*S*)-5-((*S*)-1-Acetoxy-2-(*tert*-butylamino)-2-oxoethyl)tetrahydrofuran-2-yl) methyl butyrate *anti*-7a and ((2*R*,5*S*)-5-((*R*)-1-acetoxy-2-(*tert*-butylamino)-2-oxoethyl)tetrahydrofuran-2-yl)methyl butyrate *syn*-7a. *Method A*. Aldehyde **6** (100 mg, 0.50 mmol) was dissolved in dry CH_2Cl_2 (2.5 mL) and treated with acetic acid (32 μL, 0.55 mmol) and *tert*-butyl isocyanide (62 μL, 0.55 mmol). After stirring for 40 min at rt, the mixture was directly chromatographed (PE/CH_2Cl_2/acetone 10 : 4 : 1) to give *anti*-**7a** (R_f 0.63, CH_2Cl_2/PE/EtOAc 3 : 2 : 2) and *syn*-**7a** (R_f 0.55) in 90% overall yield. Dr: 59 : 41. In order to completely separate the two diastereomers, two chromatographies were needed.

Method B. Aldehyde **6** (100 mg, 0.50 mmol) was further dried by taking it up with toluene and evaporating (the procedure was repeated twice). Then it was taken up in iPr_2O (1 mL) and treated with acetic acid (32 μL, 0.55 mmol). This solution was slowly added, during 2 h, with a syringe pump, to the mixture of *tert*-butyl isocyanide (62 μL, 0.55 mmol) and $ZnBr_2$ (freshly dried at 250 °C) (45 mg, 0.20 mmol) in iPr_2O (1 mL). At the end of addition, the mixture was further stirred for 140 min. Then the mixture was treated with 1 M HCl (12 mL) and CH_2Cl_2 (12 mL) and stirred for 10 min. The phases were separated, and the aqueous phase re-extracted twice with CH_2Cl_2. The organic phases were washed with saturated aqueous $NaHCO_3$, evaporated and chromatographed as above. Yield: 82%. Dr: 81 : 19.

Method C. Aldehyde **6** (100 mg, 0.50 mmol) was taken up in dry $CHCl_3$ (1.25 mL), treated with 3 Å molecular sieves (in rods) (20 mg) and left standing overnight. Then this solution (without the sieves) was added to zinc diacetate (101 mg, 0.55 mmol) and suddenly treated with *tert*-butyl isocyanide (62 μL, 0.55 mmol). Two washings of the flask containing the aldehyde with little $CHCl_3$ were made in order to transfer all the aldehyde. The resulting suspension was stirred at 40 °C for 285 min. Then the mixture was treated with 1 M HCl (12 mL) and CH_2Cl_2 (12 mL) and stirred for 10 min. The phases were separated, and the aqueous phase re-extracted twice with CH_2Cl_2. The organic phases were washed with saturated aqueous $NaHCO_3$, evaporated and chromatographed as above. Yield: 74%. Dr: 71 : 29.

The diastereomeric ratio was determined by ^{1}H NMR, by integration of the C*H*OAc signals, at 5.07 (*anti*) and 5.00 (*syn*). No other diastereomers (deriving from epimerization) were detected in the crude products for none of the three methods. Also, the polarimetric values of *anti* and *syn* products obtained with the three methods were identical. The absence of racemization was determined at the level of compounds *anti*-**10** (see below).

Anti-**7a** (major). Oil. R_f = 0.63 (CH_2Cl_2/PE/EtOAc 3 : 2 : 2). $[\alpha]_D$ = −6.5 (*c* 1.2, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 20 °C): δ = 6.07 (1 H, br s, N*H*), 5.07 (1 H, d, *J* = 5.2 Hz, C*H*OAc), 4.29 (1 H, td, *J* = 6.0, 3.5 Hz, 5-H), 4.16–4.09 (1 H, m, 2-H), 4.12 and 4.04 (2 H, AB part of an ABX syst., J_{AB} = 11.5, J_{AX}, J_{BX} = 4.0, 6.0 Hz, CH_2O), 2.33 (2 H, t, *J* = 7.5 Hz, COCH_2CH$_2$CH$_3$), 2.17 (3 H, s, CH_3CO), 2.04–1.94 (3 H, m, 3-H, 4-H), 1.74–1.60 (3 H, m, 3-H or 4-H and COCH$_2$CH_2CH$_3$), 1.35 (9 H, s, (CH_3)$_3$C), 0.96 (3 H, t, *J* = 7.5 Hz, CH_3CH$_2$). ^{13}C NMR (126 MHz, $CDCl_3$, 20 °C, acquired in J-MOD pulse sequence): δ = 173.6, 169.6, 166.6 (C═O), 79.1 (C-5), 77.8 (C-2), 74.3 (*C*HOAc), 66.0 (CH$_2$O), 51.5 (*C*(CH$_3$)$_3$), 36.1 (*C*H$_2$CO), 28.7 ((*C*H$_3$)$_3$C), 27.5, 27.1 (C-3, C-4), 21.0 (*C*H$_3$CO), 18.5 (CH$_3$*C*H$_2$), 13.8 (*C*H$_3$CH$_2$). I.r.: ν_{max} 2966, 2939, 1736, 1678, 1529, 1456, 1366, 1221, 1178, 1081, 1047, 999, 959, 947, 920, 887, 798 cm^{-1}. HRMS (ESI+): found 344.2059 [calcd for $C_{17}H_{30}NO_6^+$ (M + H)$^+$ 344.2068].

Syn-**7a** (minor). Oil. R_f = 0.55 (CH_2Cl_2/PE/EtOAc 3 : 2 : 2). $[\alpha]_D$ = +10.4 (*c* 0.53, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 20 °C): δ = 5.85 (1 H, br s, N*H*), 5.00 (1 H, d, *J* = 4.3 Hz, C*H*OAc), 4.34 (1 H, td, *J* = 6.8, 4.2 Hz, 5-H), 4.20–4.05 (2 H, m, 2-H, C*H*HO), 4.09 (1 H, dd, *J* = 11.5, 4.0 Hz, C*H*HO), 2.32 (2 H, t, *J* = 7.4 Hz, COCH_2CH$_2$CH$_3$), 2.18 (3 H, s, CH_3CO), 2.10–1.93 (2 H, m, 3-H, 4-H), 1.90–1.54 (4 H, m, 3-H, 4-H and COCH$_2$CH_2CH$_3$), 1.35 (9 H, s, (CH_3)$_3$C), 0.96 (3 H, t, *J* = 7.4 Hz, CH_3CH$_2$). ^{13}C NMR (75 MHz, $CDCl_3$, 20 °C): δ = 173.5, 169.7, 166.8 (C═O), 78.7 (C-2 or C-5), 77.3 (C-2 or C-5), 75.2 (*C*HOAc), 66.0 (CH$_2$O), 51.4 (*C*(CH$_3$)$_3$), 36.1 (*C*H$_2$CO), 28.6 ((*C*H$_3$)$_3$C), 28.0, 27.1 (C-3, C-4), 20.9 (*C*H$_3$CO), 18.4 (CH$_3$*C*H$_2$), 13.7 (*C*H$_3$CH$_2$). I.r.: ν_{max} 3366, 2967, 2877, 1735, 1671, 1528, 1455, 1393, 1366, 1218, 1176, 1079, 1044, 997, 932, 799, 753 cm^{-1}. HRMS (ESI+): found 344.2062 [calcd for $C_{17}H_{30}NO_6^+$ (M + H)$^+$ 344.2068].

((2*R*,5*S*)-5-((*S*)-1-Acetoxy-2-((4-(benzyloxy)phenethyl)amino)-2-oxoethyl)tetrahydrofuran-2-yl)methyl butyrate *anti*-7b and ((2*R*,5*S*)-5-((*R*)-1-acetoxy-2-((4-(benzyloxy)phenethyl)amino)-2-oxoethyl)tetrahydrofuran-2-yl)methyl butyrate *syn*-7b. They were prepared with the general procedures A, B or C, using isocyanide **14**.[51] In the case of procedure B, the % of side products *anti* and *syn*-**15b** was determined by HPLC-MS-UV. R_t: 16.97 min (**15b**, 1 diast), 17.16 min (**15b**, 1 diast.), 17.79 min (both *anti* and *syn*-**7b**). The dr was determined by ^{1}H NMR on the crude product. In the case of procedures A and C, no **15b** was detected. Pure *anti*-**7b** was best isolated from reaction under condition C. In order to obtain a sample of *syn*-**7b**, a chromatography (PE/EtOAc 1 : 1, then PE/Et_2O 1 : 6) was performed on the crude product obtained through procedure A, followed by a preparative tlc. In this way we obtained *syn*-**7b**, still contaminated by 13% of *anti*-**7a**.

Anti-**7b** (major). White solid. M.p. = 96.5–97.8 °C. R_f = 0.32 (PE/EtOAc 1 : 1). $[\alpha]_D$ = +13.4 (*c* 1.1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 20 °C): δ = 7.46–7.28 (5 H, m, aromatics of Bn), 7.10 (2 H, d, *J* = 8.6 Hz, *H meta* to OBn), 6.92 (2 H, d, *J* = 8.6 Hz, *H ortho* to OBn), 6.24 (1 H, br t, *J* = 5.5 Hz, N*H*), 5.15 (1 H, d, *J* = 4.8 Hz, C*H*OAc), 5.05 (2 H, s, CH_2Ph), 4.28 (1 H, td, *J* = 6.8, 4.8 Hz, 5-H), 4.20–4.11 (1 H, m, 2-H), 4.03 and 4.00 (2 H, AB part of an ABX syst., J_{AB} = 11.5, J_{AX}, J_{BX} = 3.7, 6.6 Hz, CH_2O), 3.57 (1 H, dq, *J* = 13.3, 6.6 Hz, NHC*H*H), 3.42 (1 H, dq, *J* = 13.3,

7.0 Hz, NHC*H*H), 2.75 (2 H, t, J = 6.9 Hz, CH_2Ar), 2.29 (2 H, t, J = 7.4 Hz, CH_2CO), 2.08 (3 H, s, CH_3CO), 2.03–1.91 (3 H, m, 3-H, 4-H), 1.72–1.57 (3 H, m, CH$_3$CH_2, 3-H or 4-H), 0.94 (3 H, t, J = 7.4 Hz, CH_3CH$_2$). ^{13}C NMR (75 MHz, $CDCl_3$, 20 °C): δ = 173.5, 169.4, 167.3 (C═O), 157.5, 137.0, 130.9 (quat.), 129.8 (*C*H *meta* to OBn), 128.6 (×2), 127.9, 127.4 (×2) (*C*H of Bn), 115.0 (*C*H *ortho* to OBn), 78.9 (C-5), 77.7 (C-2), 74.3 (*C*HOAc), 70.0 (O*C*H$_2$Ph), 65.8 (CH$_2$O), 40.5 (N*C*H$_2$), 36.0 (*C*H$_2$CO), 34.7 (*C*H$_2$Ar), 27.5, 26.9 (C-3, C-4), 20.8 (*C*H$_3$CO), 18.4 (CH$_3$*C*H$_2$), 13.6 (*C*H$_3$CH$_2$). I.r.: ν_{max} 3300, 3077, 2963, 2924, 2876, 1741, 1728, 1659, 1613, 1582, 1556, 1515, 1451, 1418, 1386, 1369, 1332, 1300, 1271, 1238, 1191, 1181, 1119, 1079, 1019, 994, 942, 911, 885, 864, 835, 810, 793, 739, 698, 673, 662, 638, 619 cm^{-1}. HRMS (ESI+): found 498.2493 [calcd for $C_{28}H_{36}NO_7^+$ (M + H)$^+$ 498.2492].

Syn-**7b** (minor). Oil. R_f = 0.22 (PE/EtOAc 1 : 1). ^{1}H NMR (300 MHz, $CDCl_3$, 20 °C): δ = 7.46–7.31 (5 H, m, aromatics of Bn), 7.11 (2 H, d, J = 8.4 Hz, *H meta* to OBn), 6.92 (2 H, d, J = 8.4 Hz, *H ortho* to OBn), 6.15 (1 H, br t, J = 5.6 Hz, N*H*), 5.11 (1 H, d, J = 3.8 Hz, C*H*OAc), 5.05 (2 H, s, CH_2Ph), 4.36 (1 H, td, J = 6.6, 4.9 Hz, 5-H), 4.20–4.07 (2 H, m, 2-H, C*H*HO), 4.04–3.95 (1 H, m, C*H*HO), 3.62–3.34 (2 H, m, NHCH_2), 2.76 (2 H, t, J = 6.9 Hz, CH_2Ar), 2.29 (2 H, t, J = 7.5 Hz, CH_2CO), 2.07 (3 H, s, CH_3CO), 2.05–1.90 (3 H, m, 3-H, 4-H), 1.85–1.75 (1 H, m, 3-H or 4-H), 1.64 (2 H, sextuplet, J = 7.5 Hz, CH_2CH$_3$), 0.93 (3 H, t, J = 7.5 Hz, CH_3CH$_2$). ^{13}C NMR (75 MHz, $CDCl_3$, 20 °C): δ = 173.6, 169.5, 167.7 (C═O), 157.5, 137.0, 131.0 (quat.), 129.8 (*C*H *meta* to OBn), 128.6 (×2), 127.9, 127.4 (×2) (*C*H of Bn), 115.0 (*C*H *ortho* to OBn), 78.6 (C-5), 77.4 (C-2), 74.9 (*C*HOAc), 70.0 (O*C*H$_2$Ph), 65.9 (CH$_2$O), 40.5 (N*C*H$_2$), 36.1 (*C*H$_2$CO), 34.6 (*C*H$_2$Ar), 28.0, 27.2 (C-3, C-4), 20.8 (*C*H$_3$CO), 18.4 (CH$_3$*C*H$_2$), 13.7 (*C*H$_3$CH$_2$). I.r.: ν_{max} 3300, 3077, 2963, 2924, 2876, 1741, 1728, 1659, 1613, 1582, 1556, 1515, 1451, 1418, 1386, 1369, 1332, 1300, 1271, 1238, 1191, 1181, 1119, 1079, 1019, 994, 942, 911, 885, 864, 835, 810, 793, 739, 698, 673, 662, 638, 619 cm^{-1}. HRMS (ESI+): found 498.2488 [calcd for $C_{28}H_{36}NO_7^+$ (M + H)$^+$ 498.2492].

(*S*)-2-(Butylamino)-1-((2*S*,5*R*)-5-((butyryloxy)methyl)tetrahydrofuran-2-yl)-2-oxoethyl benzoate *anti*-7c and (*R*)-2-(butylamino)-1-((2*S*,5*R*)-5-((butyryloxy)methyl)tetrahydrofuran-2-yl)-2-oxoethyl benzoate *syn*-7c. They were prepared with the general procedures A, B or C. The diastereomeric ratio was determined by ^{1}H NMR of the crude product. No **15c** was detected by HPLC-MS-UV or ^{1}H NMR of the crude when the reaction was carried out under conditions A and C. In order to obtain the major diastereomer in pure form, two chromatographies (PE/Et_2O 1 : 1) were performed. We also obtained some mixed fractions, that afforded, upon further chromatography with PE/Et_2O 1 : 1, compound *syn* **7c**, still containing a small amount (about 10%) of the *anti* isomer.

Anti-**7c** (major). White solid. M.p. = 101.5–102.8 °C. R_f = 0.59 (PE/Et_2O 1 : 3). $[\alpha]_D$ = +6.1 (c 1.1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 20 °C): δ = 8.11–8.06 (2 H, m, *H ortho* to CO), 7.61 (1 H, tt, J = 7.5, 1.2 Hz, *H para* to CO), 7.48 (2 H, t, J = 7.5 Hz, *H meta* to CO), 6.30 (1 H, br t, J = 6.2 Hz, N*H*), 5.44 (1 H, d, J = 5.0 Hz, C*H*OBz), 4.49 (1 H, td, J = 6.8, 5.0 Hz, 2-H), 4.20 (1 H, qd, J = 7.0, 3.8 Hz, 5-H), 4.10 and 4.01 (2 H, AB part of an ABX syst., J_{AB} = 11.6, J_{AX}, J_{BX} = 3.7, 6.3 Hz, CH_2O), 3.29 (2 H, br q, J = 6.9 Hz, CH_2NH), 2.23 (2 H, t, J = 7.4 Hz, CH_2CO), 2.11 (2 H, q, J = 7.2 Hz, 3-H), 2.07–1.94 (1 H, m, 4-H), 1.80–1.68 (1 H, m, 4-H), 1.61 (2 H, hexuplet, J = 7.4 Hz, CH_2CH$_2$CO), 1.53–1.42 (2 H, m, NHCH$_2$CH_2CH$_2$), 1.40–1.26 (2 H, m, NHCH$_2$CH$_2$CH_2), 0.92 (3 H, t, J = 7.4 Hz, CH_3CH$_2$), 0.91 (3 H, t, J = 7.4 Hz, CH_3CH$_2$). ^{13}C NMR (75 MHz, $CDCl_3$, 20 °C): δ = 173.5, 167.4, 165.2 (C═O), 133.6, 129.8 (×2), 128.6 (×2) (aromatic *C*H), 129.3 (quat.), 78.9 (C-2), 77.9 (C-5), 74.8 (*C*HOBz), 65.8 (CH$_2$O), 39.1 (N*C*H$_2$), 36.0 (*C*H$_2$CO), 31.5 (NHCH$_2$*C*H$_2$), 27.5 (C-4), 27.1 (C-3), 20.0, 18.4 (*C*H$_2$), 13.7, 13.6 (CH$_3$*C*H$_2$). I.r.: ν_{max} 3674, 3296, 3078, 2959, 2913, 2871, 1741, 1724, 1655, 1603, 1561, 1451, 1392, 1373, 1302, 1263, 1246, 1174, 1124, 1101, 1070, 1026, 992, 942, 921, 902, 891, 825, 803, 766, 744, 706, 676, 635 cm^{-1}. HRMS (ESI+): found 406.2231 [calcd for $C_{22}H_{32}NO_6^+$ (M + H)$^+$ 406.2230].

Syn-**7c** (minor). Foam. R_f = 0.50 (PE/Et_2O 1 : 3). ^{1}H NMR (300 MHz, $CDCl_3$, 20 °C): δ = 8.16–8.09 (2 H, m, *H ortho* to CO), 7.64 (1 H, tt, J = 7.5, 2.1 Hz, *H para* to CO), 7.54–7.47 (2 H, m, *H meta* to CO), 6.19 (1 H, br t, J = 5.1 Hz, N*H*), 5.44 (1 H, d, J = 3.3 Hz, C*H*OBz), 4.57 (1 H, td, J = 6.8, 3.3 Hz, 2-H), 4.25–4.15 (1 H, m, 5-H), 4.26, 4.05 (2 H, AB part of an ABX syst., J_{AB} = 10.7, J_{AX}, J_{BX} = 3.4, 6.6 Hz, CH_2O), 3.36–3.20 (2 H, m, CH_2NH), 2.27 (2 H, t, J = 7.5 Hz, CH_2CO), 2.15–1.85 (3 H, m, 3-H, 4-H), 1.67–1.55 (1 H, m, 4-H), 1.63 (2 H, hexuplet, J = 7.4 Hz, CH_2CH$_2$CO), 1.53–1.42 (2 H, m, NHCH$_2$CH_2CH$_2$), 1.40–1.26 (2 H, m, NHCH$_2$CH$_2$CH_2), 0.92 (3 H, t, J = 7.4 Hz, CH_3CH$_2$), 0.89 (3 H, t, J = 7.4 Hz, CH_3CH$_2$). ^{13}C NMR (75 MHz, $CDCl_3$, 20 °C): δ = 173.6, 167.9, 165.3 (C═O), 133.8, 129.9 (×2), 128.8 (×2) (aromatic *C*H), 129.1 (quat.), 78.8, 77.2 (C-2 and C-5), 75.2 (*C*HOBz), 66.1 (CH$_2$O), 39.1 (N*C*H$_2$), 36.1 (*C*H$_2$CO), 31.5 (NHCH$_2$*C*H$_2$), 28.1 (C-4), 27.3 (C-3), 20.0, 18.4 (*C*H$_2$), 13.7, 13.6 (CH$_3$*C*H$_2$). I.r.: ν_{max} 3674, 3296, 3078, 2959, 2913, 2871, 1741, 1724, 1655, 1603, 1561, 1451, 1392, 1373, 1302, 1263, 1246, 1174, 1124, 1101, 1070, 1026, 992, 942, 921, 902, 891, 825, 803, 766, 744, 706, 676, 635 cm^{-1}. HRMS (ESI+): found 406.2225 [calcd for $C_{22}H_{32}NO_6^+$ (M + H)$^+$ 406.2230].

((2*R*,5*S*)-5-((*S*)-1-Acetoxy-2-(benzylamino)-2-oxoethyl)tetrahydrofuran-2-yl)methyl butyrate *anti*-7d. It was prepared with the general procedures B or C. The diastereomeric ratio was determined by ^{1}H NMR of the crude product. No **15d** was detected by HPLC-MS-UV or ^{1}H NMR of the crude when the reaction was carried out under conditions C. In order to obtain the major (*anti*) isomer in pure form (from procedure C), two chromatographies (PE/Et_2O 2 : 5) were performed. We have also isolated a small amount of mixed fractions of *syn* and *anti* compounds. Due to the proximity of the two spots, we failed to obtain pure *syn* compound even through preparative tlc. Therefore, the reported ^{1}H NMR of the *syn* isomer was extrapolated from the spectrum of an enriched 57 : 43 *syn* : *anti* mixture.

Anti-**7d** (major). Foam. R_f = 0.37 (PE/EtOAc 1 : 1). $[\alpha]_D$ = +4.1 (c 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 20 °C): 7.37–7.24 (5 H, m, aromatics of Bn), 6.60 (1 H, br t, J = 5.8 Hz, N*H*), 5.18 (1 H, d, J = 5.5 Hz, C*H*OAc), 4.52, 4.46 (2 H, AB part of an ABX

syst., J_{AB} = 15.0, J_{AX}, J_{BX} = 7.0, 6.2 Hz, CH_2Ph), 4.50–4.42 (1 H, m, 5-H), 4.25–4.10 (1 H, m, 2-H), 4.05 and 4.04 (2 H, AB part of an ABX syst., J_{AB} = 11.5, J_{AX}, J_{BX} = 2.6, 7.2 Hz, CH_2O), 2.23 (2 H, t, J = 7.5 Hz, CH_2CO), 2.16 (3 H, s, CH_3CO), 2.10–1.92 (3 H, m, 3-H, 4-H), 1.76–1.63 (1 H, m, 3-H or 4-H), 1.60 (2 H, hexuplet, J = 7.5 Hz, CH_2CH$_2$CO), 0.91 (3 H, t, J = 7.4 Hz, CH_3CH$_2$). ^{13}C NMR (75 MHz, $CDCl_3$, 20 °C): δ = 173.3, 169.4, 167.5 (C=O), 138.1 (quat.), 128.7 (×2), 127.6 (×2), 127.5 (aromatic *C*H), 78.9 (C-5), 78.0 (C-2), 74.6 (*C*HOAc), 65.8 (CH$_2$O), 43.3 (NCH$_2$), 36.0 (*C*H$_2$CO), 27.5, 27.3 (C-3, C-4), 20.7 (*C*H$_3$CO), 18.3 (CH$_3$*C*H$_2$), 13.5 (*C*H$_3$CH$_2$). I.r.: ν_{max} 3274, 3093, 3036, 2966, 2920, 2873, 1736, 1665, 1652, 1589, 1565, 1538, 1497, 1454, 1417, 1395, 1371, 1334, 1309, 1274, 1235, 1175, 1118, 1076, 1040, 1029, 1008, 992, 957, 937, 912, 884, 835, 789, 770, 745, 694, 648, 610 cm^{-1}. HRMS (ESI+): found 378.1915 [calcd for $C_{20}H_{28}NO_6^+$ $(M + H)^+$ 378.1917].

Syn-**7d** (minor). Foam. R_f = 0.32 (PE/EtOAc 1 : 1). ^{1}H NMR (300 MHz, $CDCl_3$, 20 °C): 7.37–7.23 (5 H, m, aromatics of Bn), 6.50 (1 H, br t, J = 5.1 Hz, N*H*), 5.21 (1 H, d, J = 3.6 Hz, C*H*OAc), 4.52 and 4.46 (2 H, AB part of an ABX syst., J_{AB} = 15.0, J_{AX}, J_{BX} = 7.0, 6.2 Hz, CH_2Ph), 4.50–4.40 (1 H, m, 5-H), 4.25–4.10 (1 H, m, 2-H and C*H*HO), 4.05–3.94 (1 H, m, C*H*HO), 2.24 (2 H, t, J = 7.5 Hz, CH_2CO), 2.18 (3 H, s, CH_3CO), 2.10–1.92 (3 H, m, 3-H, 4-H), 1.76–1.63 (1 H, m, 3-H or 4-H), 1.61 (2 H, hexuplet, J = 7.5 Hz, CH_2CH$_2$CO), 0.91 (3 H, t, J = 7.4 Hz, CH_3CH$_2$).

((2*R*,5*S*)-5-((*S*)-1-Acetoxy-2-((4-(allyloxy)phenyl)amino)-2-oxoethyl) tetrahydrofuran-2-yl)methyl butyrate *anti*-7e. It was prepared with the general procedures B or C, using 4-(allyloxyphenyl)isocyanide.[52] The diastereomeric ratio was determined by ^{1}H NMR of the crude product. No **15e** was detected in this NMR when the reaction was carried out under conditions C. In order to obtain the major (*anti*) isomer in pure form (from procedure C), two chromatographies (PE/EtOAc 2 : 1, then PE/Et$_2$O 1 : 4) were performed on the crude derived from procedure C. We have also isolated a small amount of mixed fractions of *syn* and *anti* compounds. Due to the proximity of the two spots, we failed to obtain pure *syn* compound even through preparative tlc. Therefore, the reported ^{1}H and ^{13}C NMR of the *syn* isomer was extrapolated from the spectrum of an enriched 41 : 59 *syn* : *anti* mixture.

Anti-**7e** (major). White solid. M.p. = 105.0–107.5 °C. R_f = 0.64 (CH_2Cl_2/PE/EtOAc 3 : 2 : 2). $[\alpha]_D$ = −13.1 (*c* 0.57, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 20 °C): δ = 8.02 (1 H, s, N*H*), 7.43 (2 H, d, J = 9.0 Hz, *H meta* to OAll), 6.87 (2 H, d, J = 9.0 Hz, *H ortho* to OAll), 6.04 (1 H, tdd, J = 5.3, 10.5, 17.3 Hz, C*H*=CH$_2$), 5.40 (1 H, dq, J = 17.3, 1.6 Hz, CH=C*H*H), 5.28 (1 H, dq, J = 10.5, 1.4 Hz, CH=C*H*H), 5.18 (1 H, d, J = 5.8 Hz, C*H*OAc), 4.53 (2 H, dt, J = 5.3, 1.5 Hz, CH_2CH=CH$_2$), 4.36 (1 H, q, J = 6.6 Hz, 5-H), 4.30–4.20 (1 H, m, 2-H), 4.16 and 4.11 (2 H, AB part of an ABX syst., J_{AB} = 11.7, J_{AX}, J_{BX} = 3.4, 6.2 Hz, CH_2O), 2.25 (2 H, t, J = 7.4 Hz, CH_2CO), 2.21 (3 H, s, CH_3CO), 2.15–1.94 (3 H, m, 3-H, 4-H), 1.82–1.69 (1 H, m, 3-H or 4-H), 1.67–1.53 (2 H, m, CH_2CH$_3$), 0.91 (3 H, t, J = 7.4 Hz, CH_3CH$_2$). ^{13}C NMR (75 MHz, $CDCl_3$, 20 °C): δ = 173.6, 169.6, 165.3 (C=O), 155.5, 130.6 (quat.), 133.2 (*C*H=CH$_2$), 121.6 (*C*H *meta* to OAll), 117.7 (CH=*C*H$_2$), 115.0 (*C*H *ortho* to OAll), 78.8 (C-5), 78.2 (C-2), 74.8 (*C*HOAc), 69.1 (O*C*H$_2$CH=), 65.7 (CH$_2$O), 36.0 (*C*H$_2$CO), 27.8, 27.2 (C-3, C-4), 20.9 (*C*H$_3$CO), 18.4 (CH$_3$*C*H$_2$), 13.6 (*C*H$_3$CH$_2$). I.r.: ν_{max} 3275, 3137, 3073, 2965, 2923, 2874, 1744, 1735, 1673, 1650, 1602, 1543, 1515, 1456, 1416, 1408, 1394, 1372, 1304, 1286, 1252, 1231, 1190, 1175, 1106, 1080, 1037, 996, 947, 918, 885, 832, 809, 778, 739, 716, 689, 651, 635 cm^{-1}. HRMS (ESI+): found 420.2020 [calcd for $C_{22}H_{30}NO_7^+$ $(M + H)^+$ 420.2022].

Syn-**7e** (minor). Foam. R_f = 0.62 (CH_2Cl_2/PE/EtOAc 3 : 2 : 2). ^{1}H NMR (300 MHz, $CDCl_3$, 20 °C): δ = 7.84 (1 H, s, N*H*), 7.47 (2 H, d, J = 9.0 Hz, *H meta* to OAll), 6.87 (2 H, d, J = 9.0 Hz, *H ortho* to OAll), 6.04 (1 H, tdd, J = 5.3, 10.5, 17.3 Hz, C*H*=CH$_2$), 5.40 (1 H, dq, J = 17.3, 1.6 Hz, CH=C*H*H), 5.28 (1 H, dq, J = 10.5, 1.4 Hz, CH=C*H*H), 5.25 (1 H, d, J = 3.6 Hz, C*H*OAc), 4.53 (2 H, dt, J = 5.3, 1.5 Hz, CH_2CH=CH$_2$), 4.44 (1 H, td, J = 6.3, 3.6 Hz, 5-H), 4.32 (1 H, dd, J = 11.3, 7.2 Hz, C*H*HO), 4.30–4.20 (1 H, m, 2-H), 4.02 (1 H, dd, J = 11.3, 3.6 Hz, C*H*HO), 2.25 (2 H, t, J = 7.4 Hz, CH_2CO), 2.24 (3 H, s, CH_3CO), 2.15–1.94 (3 H, m, 3-H, 4-H), 1.82–1.69 (1 H, m, 3-H or 4-H), 1.67–1.53 (2 H, m, CH_2CH$_3$), 0.91 (3 H, t, J = 7.4 Hz, CH_3CH$_2$). ^{13}C NMR (75 MHz, $CDCl_3$, 20 °C): δ = 173.7, 169.6, 165.7 (C=O), 155.5, 130.5 (quat.), 133.2 (*C*H=CH$_2$), 121.8 (*C*H *meta* to OAll), 117.7 (CH=*C*H$_2$), 115.0 (*C*H *ortho* to OAll), 78.8 (C-5), 77.8 (C-2), 74.8 (*C*HOAc), 69.1 (O*C*H$_2$CH=), 65.8 (CH$_2$O), 36.1 (*C*H$_2$CO), 27.7, 27.3 (C-3, C-4), 20.9 (*C*H$_3$CO), 18.4 (CH$_3$*C*H$_2$), 13.6 (*C*H$_3$CH$_2$).

(*S*)-1-((2*S*,5*R*)-5-((Butyryloxy)methyl)tetrahydrofuran-2-yl)-2-(methylamino)-2-oxoethyl benzoate *anti*-7f. It was prepared with the general procedure C. The diastereomeric ratio was determined by ^{1}H NMR of the crude product. No **15f** was detected in this NMR. In order to obtain the major (*anti*) isomer in pure form (from procedure C), two chromatographies (PE/EtOAc 2 : 3 and then PE/Et$_2$O 1 : 5) were performed on the crude derived from procedure C. We have also isolated a small amount of mixed fractions of *syn* and *anti* compounds. Due to the proximity of the two spots, we failed to obtain pure *syn* compound even through preparative tlc. Therefore, the reported ^{1}H NMR spectrum was extrapolated from the spectrum of an enriched 50 : 50 *syn* : *anti* mixture.

Anti-**7f.** Yellowish solid. M.p. = 87.8–89.9 °C. R_f = 0.34 (PE/Et$_2$O 1 : 5). $[\alpha]_D$ = +7.8 (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 20 °C): δ = 8.12–8.06 (2 H, m, *H ortho* to CO), 7.61 (1 H, tt, J = 7.4, 1.3 Hz, *H para* to CO), 7.47 (2 H, t, J = 7.6 Hz, *H meta* to CO), 6.33 (1 H, br s, N*H*), 5.45 (1 H, d, J = 4.8 Hz, C*H*OBz), 4.49 (1 H, td, J = 6.8, 4.9 Hz, 2-H), 4.20 (1 H, qd, J = 6.6, 3.9 Hz, 5-H), 4.08 and 4.03 (2 H, AB part of an ABX syst., J_{AB} = 11.5, J_{AX}, J_{BX} = 3.6, 6.4 Hz, CH_2O), 2.85 (3 H, d, J = 4.9 Hz, CH_3NH), 2.23 (2 H, t, J = 7.5 Hz, CH_2CO), 2.18–1.94 (3 H, m, 3-H, 4-H), 1.82–1.66 (1 H, m, 4-H), 1.61 (2 H, hexuplet, J = 7.4 Hz, CH_2CH$_2$CO), 0.92 (3 H, t, J = 7.5 Hz, CH_3CH$_2$). ^{13}C NMR (75 MHz, $CDCl_3$, 20 °C): δ = 173.6, 168.1, 165.2 (C=O), 133.6, 129.9 (×2), 128.6 (×2) (aromatic *C*H), 129.3 (quat.), 78.9 (C-2), 77.9 (C-5), 74.9 (*C*HOBz), 65.8 (CH$_2$O), 36.0 (*C*H$_2$CO), 27.5 (C-4), 27.1 (C-3), 26.1 (*C*H$_3$NH), 18.4 (*C*H$_2$), 13.6 (CH$_3$*C*H$_2$). I.r.: ν_{max} 3676, 3294, 3098, 2956, 2932, 2877, 1718, 1662, 1603,

1559, 1467, 1451, 1418, 1401, 1385, 1367, 1352, 1308, 1295, 1256, 1200, 1190, 1178, 1165, 1136, 1125, 1098, 1078, 1071, 1046, 1026, 1016, 1009, 986, 965, 950, 937, 914, 891, 848, 835, 806, 777, 734, 707, 694, 686, 677, 632 cm^{-1}. HRMS (ESI+): found 364.1755 [calcd for $C_{19}H_{26}NO_6^+$ $(M + H)^+$ 364.1760].

Syn-**7f**. Foam. R_f = 0.33 (PE/Et_2O 1 : 5). ^1H NMR (300 MHz, $CDCl_3$, 20 °C): δ = 8.14 (2 H, d, J = 8.1 Hz, *H ortho* to CO), 7.63 (1 H, t, J = 7.4 Hz, *H para* to CO), 7.50 (2 H, t, J = 7.6 Hz, *H meta* to CO), 6.29 (1 H, br s, N*H*), 5.47 (1 H, d, J = 3.3 Hz, C*H*OBz), 4.57 (1 H, td, J = 6.6, 3.3 Hz, 2-H), 4.32 (1 H, dd, J = 11.1, 6.9 Hz, C*H*HO), 4.10–3.98 (2 H, m, 5-H, C*H*HO), 2.84 (3 H, d, J = 4.9 Hz, CH_3NH), 2.28 (2 H, t, J = 7.5 Hz, CH_2CO), 2.18–1.94 (3 H, m, 3-H, 4-H), 1.82–1.66 (1 H, m, 4-H), 1.61 (2 H, hexuplet, J = 7.4 Hz, CH_2CH_2CO), 0.92 (3 H, t, J = 7.5 Hz, CH_3CH_2).

(*S*)-2-(2-(4-Benzyloxyphenyl)ethylamino)-1-((2*S*,5*R*)-5-((butyryloxy)methyl)tetrahydrofuran-2-yl)-2-oxoethyl benzoate *anti*-7g and (*R*)-2-(2-(4-benzyloxyphenyl)ethylamino)-1-((2*S*,5*R*)-5-((butyryloxy)methyl)tetrahydrofuran-2-yl)-2-oxoethyl benzoate *syn*-7g. They were prepared with the general procedure C, using isocyanide **14**.[51] The diastereomeric ratio was determined by ^1H NMR of the crude product. No **15g** was detected in this NMR. In order to obtain the two diastereomers in pure form, two chromatographies (PE/Et_2O 1 : 2) were performed.

Anti-**7g**. White solid. M.p. = 107.0–108.2 °C. R_f = 0.53 (PE/Et_2O 1 : 3). $[\alpha]_D$ = +3.0 (c 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, 20 °C): δ = 8.03–7.98 (2 H, m, *H ortho* to CO), 7.59 (1 H, tt, J = 7.5, 1.3 Hz, *H para* to CO), 7.46 (2 H, t, J = 7.6 Hz, *H meta* to CO), 7.43–7.28 (5 H, m, C*H* of benzyl), 7.07 (2 H, d, J = 8.7 Hz, *H meta* to OBn), 6.81 (2 H, d, J = 8.7 Hz, *H ortho* to OBn), 6.30 (1 H, br t, J = 5.7 Hz, N*H*), 5.47 (1 H, d, J = 4.4 Hz, C*H*OBz), 4.97 (2 H, s, CH_2Ph), 4.46 (1 H, td, J = 6.9, 4.5 Hz, 2-H), 4.15 (1 H, qd, J = 6.4, 3.9 Hz, 5-H), 4.04 and 3.95 (2 H, AB part of an ABX syst., J_{AB} = 11.5, J_{AX}, J_{BX} = 4.0, 6.2 Hz, CH_2O), 3.64–3.40 (2 H, m, CH_2NH), 2.75 (2 H, t, J = 7.0, CH_2Ar), 2.18 (2 H, t, J = 7.4 Hz, CH_2CO), 2.14–1.91 (3 H, m, 3-H, 4-H), 1.88–1.74 (1 H, m, 4-H), 1.58 (2 H, hexuplet, J = 7.4 Hz, CH_2CH_2CO), 0.89 (3 H, t, J = 7.4 Hz, CH_3CH_2). ^{13}C NMR (75 MHz, $CDCl_3$, 20 °C): δ = 173.5, 167.3, 165.0 (C═O), 157.5, 137.0, 130.8, 129.2 (quat.), 133.6 (*C*H *meta* to CO), 129.83 (×2), 129.75 (×2), 128.6 (×3), 128.0, 127.4 (×2) (other aromatic *C*H), 115.0 (*C*H *ortho* to OBn), 79.0 (C-2), 77.8 (C-5), 74.8 (*C*HOBz), 70.0 (CH_2Ph), 65.7 (CH_2O), 40.4 (CH_2NH), 36.9 (CH_2CO), 34.7 (CH_2Ar), 27.6 (C-4), 26.9 (C-3), 18.3 (CH_2), 13.6 (CH_3CH_2). I.r.: ν_{max} 3676, 3305, 3096, 3066, 3036, 2967, 2944, 2921, 2872, 1735, 1725, 1686, 1655, 1611, 1557, 1511, 1470, 1453, 1419, 1393, 1380, 1359, 1298, 1284, 1259, 1241, 1200, 1173, 1129, 1114, 1097, 1080, 1067, 1052, 1025, 1013, 997, 927, 910, 888, 866, 836, 814, 785, 749, 728, 709, 702, 684, 663, 636, 617 cm^{-1}. HRMS (ESI+): found 560.2653 [calcd for $C_{33}H_{38}NO_7^+$ $(M + H)^+$ 560.2648].

Syn-**7g**. Foam. R_f = 0.44 (PE/Et_2O 1 : 3). $[\alpha]_D$ = −20.0 (c 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, 20 °C): δ = 8.01 (2 H, d, J = 7.2 Hz, *H ortho* to CO), 7.60 (1 H, t, J = 7.4 Hz, *H para* to CO), 7.47 (2 H, t, J = 7.8 Hz, *H meta* to CO), 7.43–7.28 (5 H, m, C*H* of benzyl), 7.06 (2 H, d, J = 8.4 Hz, *H meta* to OBn), 6.78 (2 H, d, J = 8.4 Hz, *H ortho* to OBn), 6.22 (1 H, br t, J = 5.7 Hz, N*H*), 5.45 (1 H, d, J = 3.1 Hz, C*H*OBz), 4.95 (2 H, s, CH_2Ph), 4.56 (1 H, td, J = 6.6, 3.1 Hz, 2-H), 4.25–4.12 (2 H, m, 5-H, C*H*HO), 4.04 (1 H, dd, J = 13.8, 6.9 Hz, C*H*HO), 3.51 (2 H, q, J = 6.5 Hz, CH_2NH), 2.74 (2 H, t, J = 6.7 Hz, CH_2Ar), 2.23 (2 H, t, J = 7.4 Hz, CH_2CO), 2.14–1.80 (4 H, m, 3-H, 4-H), 1.60 (2 H, hexuplet, J = 7.4 Hz, CH_2CH_2CO), 0.89 (3 H, t, J = 7.4 Hz, CH_3CH_2). ^{13}C NMR (75 MHz, $CDCl_3$, 20 °C): δ = 173.5, 167.8, 165.1 (C═O), 157.5, 137.0, 130.9, 128.9 (quat.), 133.7 (*C*H *meta* to CO), 129.8 (×3), 128.7 (×2), 128.6 (×2), 127.9, 127.4 (×2) (other aromatic *C*H), 114.9 (*C*H *ortho* to OBn), 78.8 (C-2), 77.4 (C-5), 74.9 (*C*HOBz), 69.9 (CH_2Ph), 66.1 (CH_2O), 40.4 (CH_2NH), 36.0 (CH_2CO), 34.6 (CH_2Ar), 28.1 (C-4), 27.2 (C-3), 18.4 (CH_2), 13.6 (CH_3CH_2). I.r.: ν_{max} 3676, 3305, 3096, 3066, 3036, 2967, 2944, 2921, 2872, 1735, 1725, 1686, 1655, 1611, 1557, 1511, 1470, 1453, 1419, 1393, 1380, 1359, 1298, 1284, 1259, 1241, 1200, 1173, 1129, 1114, 1097, 1080, 1067, 1052, 1025, 1013, 997, 927, 910, 888, 866, 836, 814, 785, 749, 728, 709, 702, 684, 663, 636, 617 cm^{-1}. HRMS (ESI+): found 560.2657 [calcd for $C_{33}H_{38}NO_7^+$ $(M + H)^+$ 560.2648].

(*S*)-1-((2*S*,5*R*)-5-((Butyryloxy)methyl)tetrahydrofuran-2-yl)-2-((cyclohexyl)amino)-2-oxoethyl 3-phenylpropionate *anti*-7h and (*R*)-1-((2*S*,5*R*)-5-((butyryloxy)methyl)tetrahydrofuran-2-yl)-2-((cyclohexyl)amino)-2-oxoethyl 3-phenylpropionate *syn*-7h. They were prepared with the general procedure C. The diastereomeric ratio was determined by ^1H NMR of the crude product. No **15h** was detected in this NMR. In order to obtain the two diastereomers in pure form, two chromatographies (PE/Et_2O 2 : 3) were performed.

Anti-**7h** (major). White solid. M.p. = 85.9–87.3 °C. R_f = 0.66 (PE/Et_2O 1 : 3). $[\alpha]_D$ = −9.7 (c 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, 20 °C): δ = 7.33–7.17 (5 H, m, aromatics), 6.01 (1 H, d, J = 8.2 Hz, N*H*), 5.12 (1 H, d, J = 5.2 Hz, C*H*OCO), 4.32–4.24 (1 H, m, 2-H), 4.22–4.10 (1 H, m, 5-H), 4.10 and 4.02 (2 H, AB part of an ABX syst., J_{AB} = 11.4, J_{AX}, J_{BX} = 3.7, 6.5 Hz, CH_2O), 3.80–3.65 (1 H, m, C*H*NH), 3.00 (2 H, t, J = 7.5, CH_2Ar), 2.77 (2 H, t, J = 7.5, CH_2CO), 2.32 (2 H, t, J = 7.4 Hz, CH_2CO), 2.03–1.75 (6 H, m, 3-H, 4-H, 3 *H* of cyclohexyl), 1.75–1.53 (5 H, m, 4-H and 4 *H* of cyclohexyl), 1.66 (2 H, hexuplet, J = 7.4 Hz, CH_2CH_2CO), 1.43–1.00 (3 H, m, CH_2 of cyclohexyl), 0.95 (3 H, t, J = 7.4 Hz, CH_3CH_2). ^{13}C NMR (75 MHz, $CDCl_3$, 20 °C): δ = 173.4, 171.4, 166.3, (C═O), 140.0 (quat.), 128.5 (×2), 128.2 (×2), 126.3 (aromatic *C*H), 78.8 (C-2), 77.7 (C-5), 74.2 (*C*HOCO), 65.8 (CH_2O), 47.9 (*C*HNH), 35.9 (CH_2CO butyryl), 35.5 (other CH_2CO), 32.7, 32.6, 25.4, 24.62, 24.59 (CH_2 of cyclohexyl), 30.6 (CH_2Ar), 27.3 (C-4), 26.9 (C-3), 18.3 (CH_2), 13.6 (CH_3CH_2). I.r.: ν_{max} 3676, 3294, 3064, 3027, 2964, 2924, 2852, 1739, 1650, 1606, 1548, 1501, 1454, 1440, 1419, 1394, 1363, 1305, 1267, 1246, 1230, 1171, 1117, 1073, 1031, 995, 968, 950, 918, 886, 805, 784, 770, 749, 715, 695, 674, 630 cm^{-1}. HRMS (ESI+): found 460.2702 [calcd for $C_{26}H_{38}NO_6^+$ $(M + H)^+$ 460.2699].

Syn-**7h** (minor). Oil. R_f = 0.42 (PE/Et_2O 1 : 3). $[\alpha]_D$ = +11.7 (c 0.73, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, 20 °C): δ = 7.33–7.20 (5 H, m, aromatics), 5.83 (1 H, d, J = 8.4 Hz, N*H*), 5.10 (1 H, d, J = 3.9 Hz, C*H*OCO), 4.34 (1 H, td, J = 6.6, 3.9 Hz, 2-H), 4.18–4.07 (2 H, m, 5-H, C*H*HO), 4.05–3.96 (1 H, m, C*H*HO), 3.80–3.65

(1 H, m, C*H*NH), 3.01 (2 H, t, J = 7.5, CH_2Ar), 2.78 (2 H, t, J = 7.5, CH_2CO), 2.31 (2 H, t, J = 7.4 Hz, CH_2CO), 2.05–1.75 (6 H, m, 3-H, 4-H, 3 *H* of cyclohexyl), 1.75–1.53 (5 H, m, 4-H and 4 *H* of cyclohexyl), 1.66 (2 H, hexuplet, J = 7.5 Hz, CH_2CH$_2$CO), 1.43–1.00 (3 H, m, CH_2 of cyclohexyl), 0.95 (3 H, t, J = 7.4 Hz, CH_3CH$_2$). ^{13}C NMR (75 MHz, $CDCl_3$, 20 °C): δ = 173.5, 171.6, 166.8, (C═O), 140.0 (quat.), 128.6 (×2), 128.3 (×2), 126.5 (aromatic *C*H), 78.7 (C-2), 77.4 (C-5), 74.9 (*C*HOCO), 66.0 (CH$_2$O), 48.1 (*C*HNH), 36.1 (*C*H$_2$CO butyryl), 35.7 (other *C*H$_2$CO), 32.82, 32.76, 25.5, 24.8 (×2) (*C*H$_2$ of cyclohexyl), 30.7 (*C*H$_2$Ar), 28.0 (C-4), 27.1 (C-3), 18.4 (*C*H$_2$), 13.7 (CH$_3$*C*H$_2$). I.r.: ν_{max} 3309, 3028, 2932, 2855, 1736, 1659, 1604, 1530, 1497, 1452, 1418, 1364, 1255, 1173, 1146, 1078, 1050, 997, 947, 891, 805, 785, 751, 699 cm^{-1}. HRMS (ESI+): found 460.2704 [calcd for $C_{26}H_{38}NO_6^+$ (M + H)$^+$ 460.2699].

(*S*)-1-((2*S*,5*R*)-5-((Butyryloxy)methyl)tetrahydrofuran-2-yl)-2-(*tert*-butylamino)-2-oxoethyl 3-phenylpropionate *anti*-7i and (*R*)-1-((2*S*,5*R*)-5-((butyryloxy)methyl)tetrahydrofuran-2-yl)-2-(*tert*-butylamino)-2-oxoethyl 3-phenylpropionate *syn*-7i. They were prepared with the general procedure C. The diastereomeric ratio was determined by ^{1}H NMR of the crude product. No **15i** was detected in this NMR. In order to obtain the two diastereomers in pure form, two chromatographies (PE/Et$_2$O from 6 : 7 to 2 : 3) were performed.

Anti-**7i**. Oil. R_f = 0.34 (PE/Et$_2$O 6 : 7). $[\alpha]_D$ = −10.9 (c 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 20 °C): δ = 7.33–7.17 (5 H, m, aromatics), 5.99 (1 H, s, N*H*), 5.05 (1 H, d, J = 5.2 Hz, C*H*OCO), 4.30–4.13 (2 H, m, 2-H, 5-H), 4.10 and 4.02 (2 H, AB part of an ABX syst., J_{AB} = 11.3, J_{AX}, J_{BX} = 4.1, 6.2 Hz, CH_2O), 3.05–2.91 (2 H, m, CH_2Ar), 2.80–2.71 (2 H, m, CH_2CO), 2.32 (2 H, t, J = 7.5 Hz, CH_2CO), 2.03–1.87 (3 H, m, 3-H, 4-H), 1.75–1.50 (1 H, m, 4-H), 1.66 (2 H, hexuplet, J = 7.45 Hz, CH_2CH$_2$CO), 1.31 (9 H, s, (CH_3)$_3$C), 0.95 (3 H, t, J = 7.4 Hz, CH_3CH$_2$). ^{13}C NMR (75 MHz, $CDCl_3$, 20 °C): δ = 173.3, 171.4, 166.4, (C═O), 140.1 (quat.), 128.5 (×2), 128.2 (×2), 126.3 (aromatic *C*H), 78.9 (C-2), 77.6 (C-5), 74.2 (*C*HOCO), 65.8 (CH$_2$O), 47.9 (*C*HNH), 35.9 (*C*H$_2$CO butyryl), 35.5 (other *C*H$_2$CO), 51.2 (*C*(CH$_3$)$_3$), 35.9 (*C*H$_2$CO of butyryl), 35.6 (other *C*H$_2$CO), 30.6 (*C*H$_2$Ar), 28.5 (C(*C*H$_3$)$_3$, 27.3 (C-4), 26.9 (C-3), 18.3 (*C*H$_2$), 13.6 (CH$_3$*C*H$_2$). I.r.: ν_{max} 3370, 3029, 2966, 2877, 1736, 1680, 1604, 1524, 1498, 1454, 1418, 1392, 1365, 1246, 1225, 1172, 1079, 1048, 999, 911, 888, 798, 732, 699, 646 cm^{-1}. HRMS (ESI+): found 434.2548 [calcd for $C_{24}H_{36}NO_6^+$ (M + H)$^+$ 434.2543].

Syn-**7i**. Oil. R_f = 0.22 (PE/Et$_2$O 6 : 7). $[\alpha]_D$ = +46.7 (c 0.32, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 20 °C): δ = 7.33–7.17 (5 H, m, aromatics), 5.76 (1 H, s, N*H*), 5.01 (1 H, d, J = 4.2 Hz, C*H*OCO), 4.31 (1 H, td, J = 6.6, 4.2 Hz, 2-H), 4.15–3.95 (3 H, m, 5-H, CH_2O), 3.05–2.91 (2 H, m, CH_2Ar), 2.80–2.71 (2 H, m, CH_2CO), 2.30 (2 H, t, J = 7.5 Hz, CH_2CO), 2.03–1.87 (3 H, m, 3-H, 4-H), 1.77–1.50 (1 H, m, 4-H), 1.66 (2 H, hexuplet, J = 7.5 Hz, CH_2CH$_2$CO), 1.30 (9 H, s, (CH_3)$_3$C), 0.95 (3 H, t, J = 7.4 Hz, CH_3CH$_2$). ^{13}C NMR (75 MHz, $CDCl_3$, 20 °C): δ = 173.4, 171.6, 166.8, (C═O), 140.1 (quat.), 128.6 (×2), 128.3 (×2), 126.5 (aromatic *C*H), 78.7 (C-2), 77.3 (C-5), 75.2 (*C*HOCO), 66.0 (CH$_2$O), 47.9 (*C*HNH), 35.9 (*C*H$_2$CO butyryl), 35.5 (other *C*H$_2$CO), 51.3 (*C*(CH$_3$)$_3$), 36.1 (*C*H$_2$CO of butyryl), 35.8 (other *C*H$_2$CO), 30.8 (*C*H$_2$Ar), 28.6 (C(*C*H$_3$)$_3$, 28.0 (C-4), 27.1 (C-3), 18.4 (*C*H$_2$), 13.7 (CH$_3$*C*H$_2$). I.r.: ν_{max} 3370, 3029, 2966, 2877, 1736, 1680, 1604, 1524, 1498, 1454, 1418, 1392, 1365, 1246, 1225, 1172, 1079, 1048, 999, 911, 888, 798, 732, 699, 646 cm^{-1}. HRMS (ESI+): found 434.2545 [calcd for $C_{24}H_{36}NO_6^+$ (M + H)$^+$ 434.2543].

(*S*)-1-((2*S*,5*R*)-5-((Butyryloxy)methyl)tetrahydrofuran-2-yl)-2-((2,6-dimethylphenyl)amino)-2-oxoethyl 2-methylbenzoate *anti*-7j and (*R*)-1-((2*S*,5*R*)-5-((butyryloxy)methyl)tetrahydrofuran-2-yl)-2-((2,6-dimethylphenyl)amino)-2-oxoethyl 2-methylbenzoate *syn*-7j. They were prepared with the general procedure C. The diastereomeric ratio was determined by ^{1}H NMR of the crude product. No **15j** was detected in this NMR. In order to obtain the two diastereoisomers in pure form, two chromatographies (PE/Et$_2$O 7 : 6) were performed.

Anti-**7j**. White solid. M.p. = 95.8–96.4 °C. R_f = 0.44 (PE/Et$_2$O 1 : 1). $[\alpha]_D$ = +16.6 (c 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 20 °C): δ = 8.02–7.97 (1 H, m, *H ortho* to CO), 7.64 (1 H, s, N*H*), 7.43 (1 H, td, J = 7.6, 1.2 Hz, *H para* to CO), 7.31–7.23 (2 H, m, *H meta* to CO), 7.13–7.02 (3 H, m, C*H* of dimethylphenyl), 5.48 (1 H, d, J = 6.2 Hz, C*H*OCO), 4.55 (1 H, q, J = 6.6 Hz, 2-H), 4.32–4.24 (1 H, m, 5-H), 4.18 and 4.14 (2 H, AB part of an ABX syst., J_{AB} = 11.7, J_{AX}, J_{BX} = 3.6, 6.3 Hz, CH_2O), 2.64 (3 H, s, CH_3Ar), 2.25 (6 H, s, CH_3Ar), 2.23 (2 H, t, J = 7.5 Hz, CH_2CO), 2.25–2.00 (3 H, m, 3-H, 4-H), 1.88–1.75 (1 H, m, 4-H), 1.58 (2 H, hexuplet, J = 7.4 Hz, CH_2CH$_2$CO), 0.88 (3 H, t, J = 7.4 Hz, CH_3CH$_2$). ^{13}C NMR (75 MHz, $CDCl_3$, 20 °C): δ = 173.6, 166.2, 166.1 (C═O), 140.8, 135.4 (×2), 133.1, 128.6 (quat.), 132.5, 131.8, 130.6, 128.1 (×2), 127.3, 125.8 (aromatic *C*H), 78.8 (C-2), 78.1 (C-5), 74.8 (*C*HOCO), 65.7 (CH$_2$O), 35.9 (*C*H$_2$CO), 27.9 (C-4), 27.3 (C-3), 21.7, 18.5 (×2) (*C*H$_3$Ar), 18.3 (*C*H$_2$), 13.6 (CH$_3$*C*H$_2$). I.r.: ν_{max} 3254, 3043, 2966, 2928, 2878, 1723, 1666, 1602, 1577, 1532, 1457, 1380, 1303, 1278, 1242, 1174, 1141, 1113, 1083, 1062, 996, 937, 915, 893, 851, 809, 794, 763, 732, 718, 695, 626 cm^{-1}. HRMS (ESI+): found 468.2386 [calcd for $C_{27}H_{34}NO_6^+$ (M + H)$^+$ 468.2386].

Syn-**7j**. R_f = 0.29 (PE/Et$_2$O 1 : 1). $[\alpha]_D$ = +21.3 (c 0.85, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 20 °C): δ = 8.07 (1 H, dd, J = 8.2, 1.3 Hz, *H ortho* to CO), 7.48 (1 H, td, J = 7.5, 1.2 Hz, *H para* to CO), 7.44 (1 H, s, N*H*), 7.35–7.28 (2 H, m, *H meta* to CO), 7.13–7.02 (3 H, m, C*H* of dimethylphenyl), 5.54 (1 H, d, J = 3.0 Hz, C*H*OCO), 4.65 (1 H, td, J = 6.8, 3.0 Hz, 2-H), 4.30–4.17 (3 H, m, 5-H, CH_2O), 2.67 (3 H, s, CH_3Ar), 2.24 (2 H, t, J = 7.2 Hz, CH_2CO), 2.22 (6 H, s, CH_3Ar), 2.25–1.97 (3 H, m, 3-H, 4-H), 1.88–1.73 (1 H, m, 4-H), 1.57 (2 H, hexuplet, J = 7.5 Hz, CH_2CH$_2$CO), 0.88 (3 H, t, J = 7.4 Hz, CH_3CH$_2$). ^{13}C NMR (75 MHz, $CDCl_3$, 20 °C): δ = 173.6, 166.8, 166.0 (C═O), 141.4, 135.5 (×2), 132.9, 128.0 (quat.), 133.0, 132.2, 130.5, 128.2 (×2), 127.4, 126.1 (aromatic *C*H), 78.7 (C-2), 78.6 (C-5), 75.6 (*C*HOCO), 66.1 (CH$_2$O), 36.0 (*C*H$_2$CO), 28.1 (C-4), 27.3 (C-3), 21.9, 18.4 (×2) (*C*H$_3$Ar), 18.3 (*C*H$_2$), 13.6 (CH$_3$*C*H$_2$). I.r.: ν_{max} 3254, 3043, 2966, 2928, 2878, 1723, 1666, 1602, 1577, 1532, 1457, 1380, 1303, 1278, 1242, 1174, 1141, 1113, 1083, 1062, 996, 937, 915, 893, 851, 809, 794, 763, 732, 718, 695, 626 cm^{-1}. HRMS (ESI+): found 468.2394 [calcd for $C_{27}H_{34}NO_6^+$ (M + H)$^+$ 468.2386].

(*S*)-2-((*tert*-Butyl)amino)-1-((2*S*,5*R*)-5-((butyryloxy)methyl) tetrahydrofuran-2-yl)-2-oxoethyl 2-methylbenzoate *anti*-7k and (*R*)-2-((*tert*-butyl)amino)-1-((2*S*,5*R*)-5-((butyryloxy)methyl) tetrahydrofuran-2-yl)-2-oxoethyl 2-methylbenzoate *syn*-7k. They were prepared with the general procedure C. The diastereomeric ratio was determined by ^{1}H NMR of the crude product. No **15k** was detected in this NMR. In order to obtain the two diastereomers in pure form, two chromatographies (PE/Et_2O 3 : 2) were performed.

Anti-**7k**. Oil. R_f = 0.47 (PE/Et_2O 1 : 1). $[\alpha]_D$ = +7.6 (*c* 1.5, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 20 °C): δ = 7.98–7.93 (1 H, m, *H ortho* to CO), 7.43 (1 H, td, *J* = 7.5, 1.4 Hz, *H para* to CO), 7.31–7.23 (2 H, m, *H meta* to CO), 6.13 (1 H, s, N*H*), 5.30 (1 H, d, *J* = 5.1 Hz, C*H*OCO), 4.42 (1 H, td, *J* = 6.8, 5.2 Hz, 2-H), 4.25–4.14 (1 H, m, 5-H), 4.12 and 4.02 (2 H, AB part of an ABX syst., J_{AB} = 11.4, J_{AX}, J_{BX} = 3.8, 6.4 Hz, CH_2O), 2.62 (3 H, s, CH_3Ar), 2.25 (2 H, t, *J* = 7.5 Hz, CH_2CO), 2.13–1.93 (3 H, m, 3-H, 4-H), 1.79–1.65 (1 H, m, 4-H), 1.62 (2 H, hexuplet, *J* = 7.4 Hz, CH_2CH$_2$CO), 1.36 (9 H, s, C(CH_3)$_3$), 0.92 (3 H, t, *J* = 7.4 Hz, CH_3CH$_2$). ^{13}C NMR (75 MHz, $CDCl_3$, 20 °C): δ = 173.4, 166.7, 165.9 (C═O), 140.7, 128.7 (quat.), 132.5, 131.8, 130.5, 125.9 (aromatic *C*H), 79.0 (C-2), 77.7 (C-5), 74.7 (*C*HOCO), 65.8 (CH_2O), 51.4 (*C*(CH$_3$)$_3$), 35.9 (*C*H$_2$CO), 28.7 (C(*C*H$_3$)$_3$), 27.4 (C-4), 27.1 (C-3), 21.8 (*C*H$_3$Ar), 18.3 (*C*H$_2$), 13.6 (CH$_3$*C*H$_2$). I.r.: ν_{max} 3371, 2966, 2877, 1725, 1681, 1603, 1532, 1456, 1392, 1364, 1301, 1287, 1248, 1226, 1176, 1141, 1081, 1050, 999, 918, 889, 793, 737, 698, 664 cm^{-1}. HRMS (ESI+): found 420.2389 [calcd for $C_{23}H_{34}NO_6^+$ (M + H)$^+$ 420.2386].

Syn-**7k**. Oil. R_f = 0.37 (PE/Et_2O 1 : 1). $[\alpha]_D$ = −12.7 (*c* 0.34, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 20 °C): δ = 8.00–7.95 (1 H, m, *H ortho* to CO), 7.45 (1 H, td, *J* = 7.5, 1.2 Hz, *H para* to CO), 7.31–7.23 (2 H, m, *H meta* to CO), 5.96 (1 H, s, N*H*), 5.25 (1 H, d, *J* = 4.2 Hz, C*H*OCO), 4.45 (1 H, td, *J* = 6.6, 4.2 Hz, 2-H), 4.24–4.04 (3 H, m, 5-H, CH_2O), 2.63 (3 H, s, CH_3Ar), 2.25 (2 H, t, *J* = 7.2 Hz, CH_2CO), 2.13–1.87 (3 H, m, 3-H, 4-H), 1.73–1.63 (1 H, m, 4-H), 1.62 (2 H, hexuplet, *J* = 7.4 Hz, CH_2CH$_2$CO), 1.35 (9 H, s, C(CH_3)$_3$), 0.91 (3 H, t, *J* = 7.4 Hz, CH_3CH$_2$). ^{13}C NMR (75 MHz, $CDCl_3$, 20 °C): δ = 173.5 167.1, 166.0 (C═O), 140.8, 128.6 (quat.), 132.6, 131.9, 130.5, 126.0 (aromatic *C*H), 78.8 (C-2), 77.3 (C-5), 75.3 (*C*HOCO), 66.1 (CH_2O), 51.4 (*C*(CH$_3$)$_3$), 36.0 (*C*H$_2$CO), 28.7 (C(*C*H$_3$)$_3$), 28.0 (C-4), 27.2 (C-3), 21.8 (*C*H$_3$Ar), 18.4 (*C*H$_2$), 13.6 (CH$_3$*C*H$_2$). I.r.: ν_{max} 3371, 2966, 2877, 1725, 1681, 1603, 1532, 1456, 1392, 1364, 1301, 1287, 1248, 1226, 1176, 1141, 1081, 1050, 999, 918, 889, 793, 737, 698, 664 cm^{-1}. HRMS (ESI+): found 420.2379 [calcd for $C_{23}H_{34}NO_6^+$ (M + H)$^+$ 420.2386].

(*S*)-2-((Butyl)amino)-1-((2*S*,5*R*)-5-((butyryloxy)methyl)tetrahydrofuran-2-yl)-2-oxoethyl 2-methylbenzoate *anti*-7l and (*R*)-2-((butyl)amino)-1-((2*S*,5*R*)-5-((butyryloxy)methyl)tetrahydrofuran-2-yl)-2-oxoethyl 2-methylbenzoate *syn*-7l. It was prepared with the general procedure C. The diastereomeric ratio was determined by ^{1}H NMR of the crude product. No **15l** was detected in this NMR. In order to obtain the two diastereomers in pure form, two chromatographies (PE/Et_2O 4 : 5) were performed. However, the *syn* diastereomer was still contaminated by 14% of *anti* epimer.

Anti-**7l**. White solid. M.p. = 81.2–83.0 °C. R_f = 0.43 (PE/Et_2O 1 : 2). $[\alpha]_D$ = +6.9 (*c* 1.2, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 20 °C): δ = 8.00–7.94 (1 H, m, *H ortho* to CO), 7.44 (1 H, td, *J* = 7.5, 1.4 Hz, *H para* to CO), 7.31–7.23 (2 H, m, *H meta* to CO), 6.34 (1 H, bt, *J* = 4.7 Hz, N*H*), 5.37 (1 H, d, *J* = 5.3 Hz, C*H*OCO), 4.45 (1 H, td, *J* = 6.9, 5.4 Hz, 2-H), 4.20 (1 H, qd, *J* = 6.7, 3.8 Hz, 5-H), 4.11 and 4.06 (2 H, AB part of an ABX syst., J_{AB} = 11.6, J_{AX}, J_{BX} = 3.6, 6.4 Hz, CH_2O), 3.39–3.18 (2 H, m, CH_2NH), 2.62 (3 H, s, CH_3Ar), 2.25 (2 H, t, *J* = 7.5 Hz, CH_2CO), 2.13–1.93 (3 H, m, 3-H, 4-H), 1.80–1.65 (1 H, m, 4-H), 1.62 (2 H, hexuplet, *J* = 7.5 Hz, CH_2CH$_2$CO), 1.55–1.20 (4 H, m, CH_2CH_2CH$_3$), 0.92 (3 H, t, *J* = 7.4 Hz, CH_3CH$_2$). 0.91 (3 H, t, *J* = 7.4 Hz, CH_3CH$_2$). ^{13}C NMR (75 MHz, $CDCl_3$, 20 °C): δ = 173.5, 167.5, 165.9 (C═O), 140.8, 128.6 (quat.), 132.5, 131.8, 130.6, 125.8 (aromatic *C*H), 78.9 (C-2), 77.8 (C-5), 74.6 (*C*HOCO), 65.8 (CH_2O), 39.1 (*C*H$_2$NH), 35.9 (*C*H$_2$CO), 31.5 (*C*H$_2$), 27.4 (C-4), 27.2 (C-3), 21.7 (*C*H$_3$Ar), 20.0 (*C*H$_2$), 18.3 (*C*H$_2$CH$_2$CO), 13.7, 13.6 (CH$_3$*C*H$_2$). I.r.: ν_{max} 3296, 3098, 2960, 2928, 2872, 2309, 1939, 1721, 1656, 1603, 1565, 1491, 1450, 1378, 1304, 1282, 1246, 1203, 1183, 1144, 1123, 1085, 1063, 1038, 1017, 999, 959, 942, 924, 906, 892, 872, 800, 770, 734, 697, 686, 666, 636 cm^{-1}. HRMS (ESI+): found 420.2390 [calcd for $C_{23}H_{34}NO_6^+$ (M + H)$^+$ 420.2386].

Syn-**7l**. Oil. R_f = 0.34 (PE/Et_2O 1 : 2). ^{1}H NMR (300 MHz, $CDCl_3$, 20 °C): δ = 8.05–7.99 (1 H, m, *H ortho* to CO), 7.46 (1 H, td, *J* = 7.5, 1.2 Hz, *H para* to CO), 7.34–7.24 (2 H, m, *H meta* to CO), 6.19 (1 H, bt, *J* = 6.3 Hz, N*H*), 5.38 (1 H, d, *J* = 3.9 Hz, C*H*OCO), 4.50 (1 H, td, *J* = 6.9, 3.9 Hz, 2-H), 4.24–4.00 (3 H, m, 5-H, CH_2O), 3.28 (2 H, q, *J* = 6.7 Hz, CH_2NH), 2.63 (3 H, s, CH_3Ar), 2.26 (2 H, t, *J* = 7.5 Hz, CH_2CO), 2.15–1.8 (3 H, m, 3-H, 4-H), 1.77–1.63 (1 H, m, 4-H), 1.61 (2 H, hexuplet, *J* = 7.5 Hz, CH_2CH$_2$CO), 1.55–1.20 (4 H, m, CH_2CH_2CH$_3$), 0.91 (3 H, t, *J* = 7.4 Hz, CH_3CH$_2$). 0.90 (3 H, t, *J* = 7.4 Hz, CH_3CH$_2$). ^{13}C NMR (75 MHz, $CDCl_3$, 20 °C): δ = 173.6, 168.0, 165.9 (C═O), 141.1, 128.4 (quat.), 132.7, 132.0, 130.6, 126.0 (aromatic *C*H), 78.8 (C-2), 77.2 (C-5), 74.9 (*C*HOCO), 66.0 (CH_2O), 39.1 (*C*H$_2$NH), 36.1 (*C*H$_2$CO), 31.5 (*C*H$_2$), 28.0 (C-4), 27.3 (C-3), 21.8 (*C*H$_3$Ar), 20.0 (*C*H$_2$), 18.4 (*C*H$_2$CH$_2$C═O), 13.7 (CH$_3$*C*H$_2$). I.r.: ν_{max} 3296, 3098, 2960, 2928, 2872, 2309, 1939, 1721, 1656, 1603, 1565, 1491, 1450, 1378, 1304, 1282, 1246, 1203, 1183, 1144, 1123, 1085, 1063, 1038, 1017, 999, 959, 942, 924, 906, 892, 872, 800, 770, 734, 697, 686, 666, 636 cm^{-1}. HRMS (ESI+): found 420.2387 [calcd for $C_{23}H_{34}NO_6^+$ (M + H)$^+$ 420.2386].

((2*R*,5*S*)-5-((4-Methoxyphenoxy)methyl)tetrahydrofuran-2-yl) methanol 8. A solution of monobutyrate **4** (773 mg, 3.82 mmol)(97% ee) in dry CH_2Cl_2 (30 mL) was treated with 4-methoxyphenol (1.42 g, 11.5 mmol), PPh_3 (1.50 g, 5.73 mmol) and di-*tert*-butyl azodicarboxylate (TBAD) (20 wt% in toluene, 6.6 mL, 5.73 mmol). The resulting yellow solution was stirred at 35 °C overnight and the volatile components were removed under reduced pressure. To eliminate Ph_3P═O, the crude was filtered through a silica plug, eluting with PE/EtOAc 7 : 3 and the product was collected as a crude after removal of the solvents. The resulting white solid was dissolved in MeOH (9.6 mL) and treated with 0.6 M KOH in MeOH (9.6 mL). After stirring overnight, the solvent was removed, and the residue was taken up with saturated aqueous

NH_4Cl (30 mL) and extracted with EtOAc (3 × 20 mL). The organic layer was washed with brine, evaporated to dryness and chromatographed (PE/EtOAc from 1 : 1 to 4 : 6) to afford compound **8** (884 mg, 97% over two steps) as pale-yellow oil. R_f = 0.23 (PE/EtOAc 1 : 1). $[\alpha]_D$ = −8.2 (*c* 1.06, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 6.90–6.79 (4 H, m, aromatics), 4.38–4.28 (1 H, m, C*H*CH_2OPMP), 4.20–4.11 (1 H, m, C*H*CH_2OH), 4.03 and 3.94 (2 H, AB part of ABX system, J_{AB} = 9.9 Hz, J_{AX}, J_{BX} = 3.8, 4.7 Hz, CH_2OPMP), 3.84–3.77 (1 H, m, C*H*HOH), 3.77 (3 H, s, OCH_3), 3.53 (1 H, ddd, *J* = 11.7, 7.5, 4.7 Hz, C*H*HOH), 2.22 (1 H, dd, *J* = 7.5, 5.3 Hz, O*H*), 2.12–1.87 (4 H, m, 3-H, 4-H). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 154.0, 152.8 (quat.), 115.5, 114.6 (aromatic *C*H), 80.3 (*C*HCH_2OH), 78.0 (*C*HCH_2OPMP), 70.8 (CH*C*H_2OPMP), 65.1(CH*C*H_2OH), 55.7 (O*C*H_3), 28.2, 27.1 (C-3, C-4). I.r.: ν_{max} 3435, 3049, 2917, 2873, 2060, 1591, 1506, 1457, 1288, 1226, 1180, 1034, 943, 917, 884, 823, 735, 703 cm^{-1}. HRMS (ESI+): found 239.1283 [calcd for $C_{13}H_{19}O_4^+$ $(M + H)^+$ 239.1283].

(*R*) and (*S*)-*N*-(*tert*-Butyl)-2-hydroxy-2-((2*R*,5*S*)-5-((4-methoxyphenoxy)methyl)tetrahydrofuran-2-yl)acetamide *anti*-9 and *syn*-9. Alcohol **8** (53 mg, 0.22 mmol) was oxidized following the same procedure used for **6**. Then this aldehyde was submitted to a Passerini reaction with *tert*-butyl isocyanide and acetic acid, following general method A to give, after chromatography, an unseparated diastereomeric mixture (61 : 39) (by ^{1}H NMR) of *anti* and *syn* Passerini adducts (76 mg, 90%). This mixture was taken up in MeOH (3 mL), H_2O (0.6 mL) and Et_3N (0.6 mL). After 1 h at rt, the solvent was evaporated, and the crude purified by preparative TLC (PE/Et_2O/CH_2Cl_2 2 : 3 : 2) to give pure *anti*-**9** (37.5 mg) and *syn*-**9** (24.0 mg). Overall yield: 91%.

Anti-**9**. Oil. R_f = 0.49 (PE/Et_2O/CH_2Cl_2 2 : 3 : 2). $[\alpha]_D$ = +23.6 (*c* 2, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 6.85 (4 H, s, aromatics), 6.76 (1 H, br s, NH), 4.41–4.32 (1 H, m, 2-H or 5-H), 4.27–4.18 (1 H, m, 2-H or 5-H), 4.14 (1 H, dd, *J* = 10.0, 3.3 Hz, C*H*HOAr), 4.06 (1 H, dd, *J* = 6.1, 2.5 Hz, C*H*OH), 3.91 (1 H, dd, *J* = 10.0, 3.5 Hz, C*H*HOAr), 3.83 (1 H, d, *J* = 2.6 Hz, O*H*), 3.77 (3 H, s, CH_3O), 2.14–1.97 (4 H, m, 3-H, 4-H), 1.32 (9 H, s, (C(CH_3)$_3$)). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 170.4 (*C*═O), 154.2, 152.4 (aromatic quat.), 115.4, 114.7 (aromatic *C*H), 80.7, 78.3 (C-2, C-5), 72.1 (*C*HOH), 70.0 (*C*H_2OAr), 55.7 (O*C*H_3), 50.9 (*C*(CH$_3$)$_3$), 28.6 (C(*C*H$_3$)$_3$), 26.9, 26.8 (C-3, C-4). HRMS (ESI+): found 338.2005 [calcd for $C_{18}H_{28}NO_5^+$ $(M + H)^+$ 338.2000].

Syn-**9**. Oil. R_f = 0.36 (PE/Et_2O/CH_2Cl_2 2 : 3 : 2). $[\alpha]_D$ = −60.1 (*c* 1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 6.91–6.81 (4 H, m, aromatics), 6.57 (1 H, br s, NH), 4.44 (1 H, td, *J* = 6.7, 3.5 Hz, 2-H), 4.37–4.29 (1 H, m, 5-H), 4.14 (1 H, dd, *J* = 9.9, 3.3 Hz, C*H*HOAr), 3.93 (1 H, dd, *J* = 6.3, 3.6 Hz, C*H*OH), 3.91 (1 H, dd, *J* = 10.0, 3.6 Hz, C*H*HOAr), 3.78 (1 H, d, *J* = 6.3 Hz, O*H*), 3.77 (3 H, s, CH_3O), 2.16–1.9 (4 H, m, 3-H, 4-H), 1.34 (9 H, s, (C(CH_3)$_3$)). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 171.0 (*C*═O), 154.3, 152.6 (aromatic quat.), 115.5, 114.8 (aromatic *C*H), 80.0, 78.0 (C-2, C-5), 73.3 (*C*HOH), 70.7 (*C*H_2OAr), 55.7 (O*C*H_3), 50.9 (*C*(CH$_3$)$_3$), 28.7 (C(*C*H$_3$)$_3$), 28.1, 27.7 (C-3, C-4). HRMS (ESI+): found 338.1998 [calcd for $C_{18}H_{28}NO_5^+$ $(M + H)^+$ 338.2000].

(*S*)-*N*-(*tert*-Butyl)-2-hydroxy-2-((2*S*,5*R*)-5-(hydroxymethyl)tetrahydrofuran-2-yl)acetamide *anti*-10. Triethylamine (0.3 mL) and H_2O (0.3 mL) were added to a stirred solution of *anti*-**7a** (105 mg, 0.31 mmol) in MeOH (1.4 mL). The reaction was stirred at room temperature overnight and concentrated. The residue was chromatographed with CH_2Cl_2/*c*Hex/EtOAc (3 : 2 : 2) to give *anti*-**10** (63 mg, 89%), as a colourless oil. The enantiomeric excess (>99%) was determined by HPLC on a chiral stationary phase. Conditions: column Daicel Chiral Pak AD (250 × 4.6 mm); detector DAD (210 nm). Isocratic elution with *n*-hexane/isopropanol 85 : 15. Temperature: 25 °C. R_t: *anti*-**10**: 7.18 min. *anti-ent*-**10**: 9.38 min. $[\alpha]_D$ = −49.3 (*c* 1, $CHCl_3$). R_f = 0.22 (EtOAc/*c*Hex 4 : 1). ^{1}H NMR (300 MHz, $CDCl_3$, 20 °C): δ = 6.70 (1 H, br s, N*H*), 4.27–4.20 (1 H, m, 2-H), 4.20–4.08 (1 H, m, 5-H), 4.11 (1 H, d, *J* = 5.1 Hz, C*H*-OH), 3.88 (1 H, dd, *J* = 11.4, 2.9 Hz, C*H*HOH), 3.59 (1 H, dd, *J* = 11.4, 3.7 Hz, C*H*HOH), 2.00–1.86 (4 H, m, 3-H, 4-H), 1.37 (9 H, s, C(CH_3)$_3$). ^{13}C NMR (75 MHz, $CDCl_3$, 20 °C): δ = 170.4 (*C*═O), 80.8 (C-2), 80.0 (C-5), 72.8 (*C*HOH), 64.6 (*C*H_2OH), 51.0 (*C*(CH$_3$)$_3$), 28.7 (C(*C*H$_3$)$_3$), 26.7, 26.5 (C-3, C-4). I.r.: ν_{max} 3331, 3313, 3294, 3271, 3223, 3204, 3148, 3101, 3090, 2966, 2934, 2920, 2907, 2876, 1649, 1529, 1456, 1394, 1364, 1294, 1225, 1130, 1103, 1047, 1014, 677, 648, 621 cm^{-1}. HRMS (ESI+): found 232.1545 [calcd for $C_{11}H_{22}NO_4^+$ $(M + H)^+$ 232.1543].

(*R*)-*N*-(*tert*-Butyl)-2-hydroxy-2-((2*R*,5*S*)-5-(hydroxymethyl)tetrahydrofuran-2-yl)acetamide *anti-ent*-10. A solution of *anti*-**9** (9.6 mg, 0.028 mmol) in CH_3CN (0.47 mL) and H_2O (0.14 mL) was cooled at 0 °C, and treated with $(NH_4)_2Ce(NO_3)_6$ (39 mg, 0.071 mmol). After 15 min the reaction was quenched by addition of saturated aqueous $NaHCO_3$. Extraction with CH_2Cl_2 evaporation, and preparative TLC (EtOAc) gave the title compound (4.3 mg, 66%). The enantiomeric excess (98%) was determined by HPLC on a chiral stationary phase. For conditions see the preparation of *anti-ent*-**10**. $[\alpha]_D$ = +50.8 (*c* 1, $CHCl_3$). The ^{1}H NMR spectrum was identical to that of *anti*-**10**, and different from that of *syn*-**10** (see the preparation of *syn*-**22**).

(*S*)-2-(*tert*-Butylamino)-1-((2*S*,5*R*)-5-(hydroxymethyl)tetrahydrofuran-2-yl)-2-oxoethyl acetate 21. A solution of *anti*-**7a** (95 mg, 0.28 mmol) in THF (0.3 mL) and phosphate buffer 0.1 M pH 7 (1.1 mL) was treated with lipase from *Candida antarctica* (CAL-B) (19 mg), and stirred at r.t. for 4 d. Then the enzyme was filtered washing with EtOAc/H_2O. The phases were separated and the aqueous phase re-extracted with EtOAc (20 mL × 3). The organic phase was finally concentrated and chromatographed (EtOAc/*c*Hex 3 : 1), to give alcohol **21** as a white solid (57 mg, 75%). $[\alpha]_D$ = −6.7 (*c* 1, $CHCl_3$). M.p. = 110.0–111.4 °C. R_f = 0.21 (EtOAc/*c*Hex 2 : 1). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 6.10 (1 H, br s, NH), 5.12 (1 H, d, *J* = 4.6 Hz, C*H*OAc), 4.21 (1 H, td, *J* = 6.7, 4.7 Hz, 2-H), 4.16–4.08 (1 H, m, 5-H), 3.77 and 3.46 (2 H, part AB of ABX syst., J_{AB} = 11.9, J_{AX}, J_{BX} = 2.7, 3.9 Hz, CH_2OH), 2.18 (3 H, s, CH_3CO), 2.15–1.85 (4 H, m, 3-H, 4-H), 1.37 (9 H, s, ((CH_3)$_3$)). ^{13}C NMR (126 MHz, $CDCl_3$, 25 °C, acquired in J-MOD pulse sequence): δ = 169.3, 167.1 (C═O), 80.7 (C-2), 79.5 (C-5), 74.5 (*C*HOAc), 64.4 (*C*H_2OH), 51.5 (*C*(CH$_3$)$_3$), 28.6 (C(*C*H$_3$)$_3$), 28.5, 25.9 (C-3, C-4), 21.0 (*C*H_3CO).

IR: ν_{max} = 3395, 3327, 3285, 2968, 2928, 1742, 1670, 1649, 1560, 1458, 1367, 1225, 1103, 1070, 1047 cm^{-1}. HRMS (ESI+): found 274.1638 [calcd for $C_{13}H_{24}NO_5^+$ $(M + H)^+$ 274.1649].

(1*S*,2*S*,5*R*)-*N*-(*tert*-Butyl)-3,8-dioxabicyclo[3.2.1]octane-2-carboxamide *anti*-22 and (1*S*,2*R*,5*R*)-*N*-(*tert*-butyl)-3,8-dioxabicyclo [3.2.1]octane-2-carboxamide *syn*-22. Triethylamine (0.6 mL) and H_2O (0.6 mL) were added to a stirred solution of a 76 : 24 mixture of *anti*-7**a** and *syn*-7**a** (273 mg, 0.80 mmol) in MeOH (2.8 mL). The reaction was stirred at room temperature overnight and concentrated. The residue was chromatographed with CH_2Cl_2/*c*Hex/EtOAc (3 : 2 : 2) to give a mixture of *anti*-**10** and *syn*-**10** (141 mg, 77%), as a colourless oil. R_f = 0.22 (EtOAc/*c*Hex 4 : 1). From the NMR of this mixture we could extrapolate the ^{1}H NMR of the minor *syn* isomer: ^{1}H NMR (500 MHz, $CDCl_3$, 20 °C): δ = 6.76 (1 H, br s, N*H*), 4.30 (1 H, td, J = 7.0, 3.5 Hz, 5-H), 4.20–4.00 (1 H, m, 2-H), 3.89 (1 H, d, J = 3.5 Hz, C*H*OH), 3.81 and 3.53 (2 H, part. AB of ABX sist., J_{AB} = 11.6, J_{AX}, J_{BX} = 2.7, 3.4 Hz, CH_2O), 2.04–1.84 (4 H, m, 3-H and 4-H), 1.35 (9 H, s, (CH_3)$_3$C). ^{13}C NMR (126 MHz, $CDCl_3$, 25 °C): δ = 171.7 (C=O), 80.2, 80.0 (C-2 and C-5), 73.8 (*C*HOH), 65.1 (*C*H_2O), 51.2 (*C*(CH$_3$)$_3$), 28.8 ((*C*H$_3$)$_3$C), 28.2, 27.3 (C-3 and C-4). This mixture (0.61 mmol) was taken up in dry THF (35 mL) at room temperature and treated with triphenylphosphine (240 mg, 0.91 mmol) and diethyl azodicarboxylate (60% in toluene, 416 μL, 0.91 mmol). The mixture was stirred at room temperature for 3.5 h and then concentrated. The crude product was eluted from a column of silica gel with *c*Hex/EtOAc (4 : 1 to pure EtOAc) to give *anti*-**22** (59 mg) and *syn*-**22** (20 mg) (minor) (overall yield = 61%) separately.

Anti-**22**. White solid. $[\alpha]_D$ = −55.7 (*c* 1, $CHCl_3$). M.p. = 55.6–57.1 °C. R_f = 0.27 (*c*Hex/EtOAc 4 : 1). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 6.32 (1 H, br s, NH), 4.58 (1 H, d, J = 6.7 Hz, 1-H), 4.21 (1 H, d, J = 3.6 Hz, 5-H), 4.09 (1 H, s, 2-H), 3.85 and 3.57 (2 H, AB syst., J = 11 Hz, 4-H), 1.98–1.74 (4 H, m, H-6 and H-7), 1.36 (9 H, s, C(CH_3)$_3$). ^{13}C NMR (126 MHz, $CDCl_3$, 25 °C, acquired in J-MOD pulse sequence): δ = 167.8 (C=O), 78.3, 76.2 (C-1 and C-5), 74.5 (C-2), 71.6 (C-4), 50.9 (*C*(CH$_3$)$_3$), 28.8 (C(*C*H$_3$)$_3$), 27.1, 24.8 (C-6, C-7). IR ν_{max} = 3410, 2962, 2916, 2868, 1747, 1670, 1522, 1456, 1364, 1285, 1275, 1227, 1122, 1082, 1065, 1051, 1032, 1007, 995, 935, 891, 876, 818, cm^{-1}. HRMS (ESI+): found 214.1441 [calcd for $C_{11}H_{20}NO_3^+$ $(M + H)^+$ 214.1438].

Syn-**22**. Foam. R_f = 0.20 (*c*Hex/EtOAc 4 : 1). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 6.56 (1 H, br s, NH), 4.90 (1 H, d, J = 6.6 Hz, 1-H), 4.21 (1 H, d, J = 6.0 Hz, 5-H), 3.90 (1 H, dd, J = 10.8, 1.8 Hz, 4-H), 3.69 (1 H, s, 2-H), 3.44 (1 H, dd, J = 10.8, 1.8 Hz, 4-H), 2.10–1.95 (4 H, m, H-6 and H-7), 1.40 (9 H, s, C(CH_3)$_3$). ^{13}C NMR (126 MHz, $CDCl_3$, 25 °C, acquired in J-MOD pulse sequence): δ = 168.6 (C=O), 78.1, 74.2 (C-1 and C-5), 73.5 (C-2), 68.9 (C-4), 51.0 (*C*(CH$_3$)$_3$), 28.8 (C(*C*H$_3$)$_3$), 27.6, 26.1 (C-6, C-7). IR ν_{max} = 2962, 2916, 2865, 1747, 1673, 1522, 1458, 1364, 1275, 1227, 1122, 1082, 1064, 1040, 1032, 1010, 995, 930, 877, 818 cm^{-1} HRMS (ESI+): found 214.1439 [calcd for $C_{11}H_{20}NO_3^+$ $(M + H)^+$ 214.1438].

Theoretical calculations. Before starting DFT simulations a conformational analysis of aldehyde **6** was carried out with the Macromodel software (Schrödinger Release 2018-4: MacroModel, Schrödinger, LLC, New York, NY, 2018). In particular, the OPLS3[53] force field was used to describe the molecule surrounded by an implicit solvent model of $CHCl_3$. All the sampling parameters have been set to the default values.

All the conformers within a potential energy difference less than 3 kcal mol^{-1} from the absolute minimum were then optimized by DFT calculations. During these minimizations, the energy of the system was described by Density Functional Theory (DFT) using the B3LYP functional[54–56] and the LACVP**$^+$ basis set. The convergence parameters were left at the default values. All the DFT calculations were run by the Jaguar program (Schrödinger Release 2018-2: Jaguar, Schrödinger, LLC, New York, NY, 2018). Also in this case the solvent effects were described by the Poisson Boltzmann Finite element method (PBF) $CHCl_3$ solvent model. The same computational set-up was used in all the subsequent DFT runs.

The conformer of **6** with the lowest energy was then used to build a model of the possible transition states including **6**, zinc acetate and methylisocyanide. To take into account all the possible attack trajectories to the aldehyde group, the isocyanide was initially placed on the two sides of the plane defined by the atoms of the aldehyde group. During these calculations the distance between the zinc ion and the aldehyde oxygen, the zinc ion and the isocyanide carbon, the aldehyde carbon and the isocyanide carbon, were firstly restrained to an optimal value of 2.5 Å. Finally, the two models were structurally optimized without any restraint.

Then a relaxed potential energy scan (RPES) was carried out considering the distance between the carbonyl carbon atom and the carbon atom of the isocyanide as collective variable (CV). In particular, the distance has been sequentially shortened of 0.4 Å from an initial value of 5 Å to a final value of 1.4 Å. After every movement, the resulting structure has been optimized by energy minimization blocking the CV distance at the desired value and leaving the other atoms free to move. Finally, the structure corresponding to a CV of 1.4 Å was optimized without any restraint to obtain the structure showed in Fig. 1C.

The Wiberg bond orders were calculated by their Jaguar implementation.[57]

Conflicts of interest

There are no conflicts to declare.

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